REMARKS

Claims 1-10 are pending in the present application. Claims 3 and 4 are rejected under 35 U.S.C. § 101, first paragraph. Claims 1-2, 5, 7-10 are rejected under U.S.C. § 112 first paragraph. Claim 9 is rejected under 35 U.S.C. § 112 second paragraph and claim 6 is objected to as being dependent upon a rejected claim. Applicants have canceled claims 9 and 10 and added new claim 11. No new matter has been inserted through these amendments and all of the amendments are fully supported by the specification as further discussed in detail below. The rejections are respectfully traversed below.

Rejection of Claims 3 and 4, under 35 U.S.C. § 101

Claims 3 and 4 are rejected under 35 U.S.C. § 101 as being directed to nonstatutory subject matter. The Examiner insists that the claims disclose natural products that were not isolated by a process or in pure form. Applicants respectfully disagree, with the Examiner's assessment. The Examiner clearly states on page 3 of the Office Action that claim 6, a process claim, yields a compound (IV), which is "novel and unobvious". It is presumed that the Examiner understands that compound (IV) happens to be the matter disclosed in claim 4, which has been isolated in a pure form by the process described in claim 6 (and claim 5). It is well known that the Patent and Trademark Office and the courts hold discovered natural substances that are "isolated and purified" as patentable. See *Fed. Regist.* 66, 1092-1097 (2001), and see in particular the discussion found on page 1093, second column (copy attached). The specification is clear by way of examples that compound (IV) is isolated and is in pure form. Claim 3 shows a compound (III) that is structurally the same as compound (IV), but with undefined stereochemistry.

For these reasons Applicants assert that the rejection of claims 3 and 4 under 35 U.S.C. § 101 is not supported, and that claims 3 and 4 meet the requirements of 35 U.S.C. § 101. Withdrawal of this rejection is respectfully requested.

Rejection of Claims 1-2, 5 and 7-10 under 35 U.S.C. § 112 first paragraph

Claims 1-2, 5 and 7-10 are rejected under 35 U.S.C. § 112, first paragraph for lack of enablement because the specification fails to provide enablement for compounds other than wherein R_1 and R_2 form a dioxolane ring. The Examiner opines, "The cleavage of the dioxolane ring or to expand the ring size of the same to form the claimed compounds does require additional research and experimentation for one skilled in the art. A textbook teaching is seemed insufficient."

Applicants disagree and assert that at the time the application was filed sufficient prior art existed to enable the invention. The MPEP states at § 2164.05 (a): "The specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and available to the public." And, additionally states: "The state of the art existing at the filing date of the application is used to determine whether a particular disclosure is enabling as of the filing date."

Attached to this response are references, which predate the filing date of the instant application and provide proof that the state of the art was at an enabling level so as to allow one skilled in the art to practice the invention. Thus, *J. Org. Chem.* 200, 65, 6179-6186 at page 6182, Table 2, entry 12 shows the cleavage of benzodioxolane to catechol (*o*-dihydroxybenzene) with $HSiEt_3$/Cat.-$B(C_6F_5)_3$; *Synthesis* 1982, 12, 1048-1050 at page 1049, Table 2, 2nd entry also shows a cleavage of benzodioxolane to catechol using Me_3Si.

Regarding expansion of the ring size, that is synthesizing a (C_2-C_6)alkylene cyclic ether, Applicants offer the following in support: *J. Org Chem.* 1987, 52, 5616-5621, at page 5616, in the right column the reaction scheme shows the transformation of a catechol to a C_2-alkylene cyclic ether with 1,2-dibromoethane and base; *Synthetic Communications*, 2001, 31(1), 1-7 at page 3 teaches the synthesis of (C_2-C_5)alkylene cyclic ethers by reacting catechols with appropriate dibromoalkanes in the presence of a base and catalyst (quarternary ammonium salts) to give the desired compounds. Finally, *J. Med. Chem.*, 2003, 46 (25), 5484-5504 at page 5490, in Scheme 18, illustrates another example of synthesizing a C_2-alkylene cyclic ether (see sequence of compound no.72→73→74). Thus, Applicants respectively maintain that it is clear, from the references cited above that the level of skill in the art at the time the application was filed was sufficient to enable the instant invention.

Accordingly, Applicants respectfully submit that claims 1-2, 5 and 7-10 satisfy the requirements under 35 U.S.C. § 112 first paragraph. Withdrawal of this rejection is respectfully requested.

Rejection of Claim 9 under 35 U.S.C. § 112 second paragraph

Claim 9 was rejected under 35 U.S.C. § 112 second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner states that the term "inhibiting c-maf and NFAT" stands for a medical function not a disease. Applicants have cancelled claims 9 and 10 and have introduced new claim 11, which is directed to specific diseases.

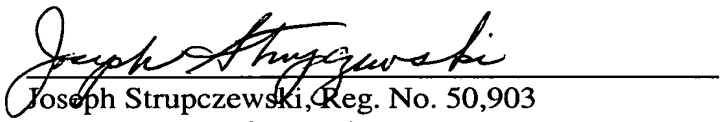
In view of the above noted amendment, Applicants believe that the rejection of claim 9 under 35 U.S.C. § 112 second paragraph is rendered moot.

Conclusion

For all the reasons presented above Applicants believe claims 1 to 9 are now in condition for allowance. Action to that end is requested. In the event the Examiner wishes to contact the undersigned regarding any matter, please call (collect if necessary) the telephone number listed below.

Applicant believes that there are no fees due for this Rule 111 Amendment. However, if the Commissioner deems that fees are due, please charge these fees to Deposit Account No. **18-1982** for Aventis Pharmaceuticals Inc., Bridgewater, NJ. Please credit any overpayment to Deposit Account No. **18-1982**.

Respectfully submitted,



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Docket No. DEAV2002/0054

Attachments: *Fed. Regist.* 66, 1092-1097 (2001); *J. Org. Chem.* 200, 65, 6179-6186; *Synthesis* 1982, 12, 1048-1050; *J. Org Chem.* 1987, 52, 5616-5621; *Synthetic Communications*, 2001, 31(1), 1-7; *J. Med. Chem.*, 2003, 46 (25), 5484-5504.

DEPARTMENT OF COMMERCE

National Oceanic and Atmospheric Administration

Fair Market Value Analysis for a Fiber Optic Cable Permit in National Marine Sanctuaries

AGENCY: Office of National Marine Sanctuaries (ONMS), National Ocean Service (NOS), National Oceanic and Atmospheric Administration (NOAA), Department of Commerce (DOC).

ACTION: Notice of availability.

SUMMARY: Notice is hereby given that NOAA is requesting comments on the report "Fair Market Value Analysis for a Fiber Optic Cable Permit in National Marine Sanctuaries" and two peer reviews of this report. The report and peer reviews are available for download at http://www.sanctuaries.nos.noaa.gov/news/newsbboard/newsbboard.html or by requesting an electronic or hard copy. Requests can be made by sending an email to submarine.cables@noaa.gov (subject line "Request for Fair Market Value Analysis") or by calling Matt Brookhart at (301) 713–3125 x140.

DATES: Comments on this notice must be received by January 18, 2001.

ADDRESSES: Address all comments regarding this notice to Matt Brookhart, Conservation Policy and Planning Branch, Office of National Marine Sanctuaries, 1305 East-West Highway, 11th Floor, Silver Spring, MD 20910, Attention: Fair Market Value Analysis. Comments may also be submitted by email to: *submarine.cables@noaa.gov,* subject line "Fair Market Value Analysis."

FOR FURTHER INFORMATION CONTACT: Helen Golde, (301) 713–3125 x152.

SUPPLEMENTARY INFORMATION: The Office of National Marine Sanctuaries has issued several special-use permits to companies seeking to install fiber optic cables in National Marine Sanctuaries. The Sanctuary statute allows ONMS to permit the presence of cables on the sanctuaries' seafloor should it decide to do so. If an application is approved, ONMS may collect certain administrative and monitoring fees. In addition, ONMS is entitled to receive fair market value for the permitted use of sanctuary resources.

The report "Fair Market Value Analysis for a Fiber Optic Cable Permit in National Marine Sanctuaries" presents an assessment of fair market value for the use of National Marine Sanctuary resources for a fiber optic cable. Proper stewardship of sanctuary resources and open and equitable relations with telecommunication industry interests require a clear and consistent policy in this matter. The content of this report is based on dozens of industry and government sources and draws on the collaboration and review of numerous experts in the business, legal and technical arenas.

Once finalized, the fee structure proposed in this report will be used to assess fees (as stated in their respective special use permits) for cables already installed in the Olympic Coast and Stellwagen Bank National Marine Sanctuaries. In addition, this structure will provide the basis for future fair market value assessment of submarine cable permit applications in National Marine Sanctuaries. Comments on the report and peer reviews should focus on the methodology employed and the conclusions that it reached.

Dated: December 29, 2000.

John Oliver,

Chief Financial Officer, National Ocean Service.

[FR Doc. 01–387 Filed 1–4–01; 8:45 am]

BILLING CODE 3510–08–P

DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

[Docket No. 991027289–0263–02]

RIN 0651–AB09

Utility Examination Guidelines

AGENCY: United States Patent and Trademark Office, Commerce.

ACTION: Notice.

SUMMARY: The United States Patent and Trademark Office (USPTO) is publishing a revised version of guidelines to be used by Office personnel in their review of patent applications for compliance with the "utility" requirement of 35 U.S.C. 101. This revision supersedes the Revised Interim Utility Examination Guidelines that were published at 64 FR 71440, Dec. 21, 1999; 1231 O.G. 136 (2000); and correction at 65 FR 3425, Jan. 21, 2000; 1231 O.G. 67 (2000).

DATES: The Guidelines are effective as of January 5, 2001.

FOR FURTHER INFORMATION CONTACT: Mark Nagumo by telephone at (703) 305–8666, by facsimile at (703) 305–9373, by electronic mail at "mark.nagumo@uspto.gov," or by mail marked to his attention addressed to the Office of the Solicitor, Box 8, Washington, DC 20231; or Linda Therkorn by telephone at (703) 305–9323, by facsimile at (703) 305–8825, by electronic mail at "linda.therkorn@uspto.gov," or by mail marked to her attention addressed to Box Comments, Commissioner for Patents, Washington, DC 20231.

SUPPLEMENTARY INFORMATION: As of the publication date of this notice, these Guidelines will be used by USPTO personnel in their review of patent applications for compliance with the "utility" requirement of 35 U.S.C. 101. Because these Guidelines only govern internal practices, they are exempt from notice and comment rulemaking under 5 U.S.C. 553(b)(A).

I. Discussion of Public Comments

The Revised Interim Utility Examination Guidelines published at 64 FR 71440, Dec. 21, 1999; 1231 O.G. 136, Feb. 29, 2000, with a correction at 65 FR 3425, Jan. 21, 2000; 1231 O.G. 67, Feb. 15, 2000, requested comments from the public. Comments were received from 35 individuals and 17 organizations. The written comments have been carefully considered.

Overview of Comments

The majority of comments generally approved of the guidelines and several expressly stated support for the three utility criteria (specific, substantial, and credible) set forth in the Guidelines. A few comments addressed particular concerns with respect to the coordinate examiner training materials that are available for public inspection at the USPTO website, *www.uspto.gov.* The comments on the training materials will be taken under advisement in the revision of the training materials. Consequently, those comments are not specifically addressed below because they do not impact the content of the Guidelines. Comments received in response to the request for comments on the "Revised Interim Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶1 'Written Description' Requirement," 64 FR 71427, Dec. 21, 1999; 1231 O.G. 123, Feb. 29, 2000, which raised issues pertinent to the utility requirement are also addressed below.

Responses to Specific Comments

(1) *Comment:* Several comments state that while inventions are patentable, discoveries are not patentable. According to the comments, genes are discoveries rather than inventions. These comments urge the USPTO not to issue patents for genes on the ground that genes are not inventions. *Response:* The suggestion is not adopted. An inventor can patent a discovery when the patent application satisfies the statutory requirements. The U.S.

Constitution uses the word "discoveries" where it authorizes Congress to promote progress made by inventors. The pertinent part of the Constitution is Article 1, section 8, clause 8, which reads: "The Congress shall have power * * * To promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries."

When Congress enacted the patent statutes, it specifically authorized issuing a patent to a person who "invents or discovers" a new and useful composition of matter, among other things. The pertinent statute is 35 U.S.C. 101, which reads: "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title." Thus, an inventor's discovery of a gene can be the basis for a patent on the genetic composition isolated from its natural state and processed through purifying steps that separate the gene from other molecules naturally associated with it.

If a patent application discloses only nucleic acid molecular structure for a newly discovered gene, and no utility for the claimed isolated gene, the claimed invention is not patentable. But when the inventor also discloses how to use the purified gene isolated from its natural state, the application satisfies the "utility" requirement. That is, where the application discloses a specific, substantial, and credible utility for the claimed isolated and purified gene, the isolated and purified gene composition may be patentable.

(2) *Comment:* Several comments state that a gene is not a new composition of matter because it exists in nature, and/or that an inventor who isolates a gene does not actually invent or discover a patentable composition because the gene exists in nature. These comments urge the USPTO not to issue patents for genes on the ground that genes are products of nature. Others state that naturally occurring DNAs are part of our heritage and are not inventions. Another comment expressed concern that a person whose body includes a patented gene could be guilty of patent infringement. *Response:* The comments are not adopted. A patent claim directed to an isolated and purified DNA molecule could cover, *e.g.*, a gene excised from a natural chromosome or a synthesized DNA molecule. An isolated and purified DNA molecule that has the same sequence as a naturally occurring gene is eligible for a patent because (1) an excised gene is eligible for a patent as a composition of matter or as an article of manufacture because that DNA molecule does not occur in that isolated form in nature, or (2) synthetic DNA preparations are eligible for patents because their purified state is different from the naturally occurring compound.

Patenting compositions or compounds isolated from nature follows well-established principles, and is not a new practice. For example, Louis Pasteur received U.S. Patent 141,072 in 1873, claiming "[y]east, free from organic germs of disease, as an article of manufacture." Another example is an early patent for adrenaline. In a decision finding the patent valid, the court explained that compounds isolated from nature are patentable: "even if it were merely an extracted product without change, there is no rule that such products are not patentable. Takamine was the first to make it [adrenaline] available for any use by removing it from the other gland-tissue in which it was found, and, while it is of course possible logically to call this a purification of the principle, it became for every practical purpose a new thing commercially and therapeutically. That was a good ground for a patent." *Parke-Davis & Co.* v. *H. K. Mulford Co.*, 189 F. 95, 103 (S.D.N.Y. 1911) (J. Learned Hand).

In a more recent case dealing with the prostaglandins PGE_2 and PGE_3, extracted from human or animal prostate glands, a patent examiner had rejected the claims, reasoning that "inasmuch as the 'claimed compounds are naturally occurring' * * * they therefore 'are not 'new' within the connotation of the patent statute.'" *In re Bergstrom*, 427 F.2d 1394, 1397, 166 USPQ 256, 259 (CCPA 1970). The Court reversed the Patent Office and explained the error: "what appellants claim—pure PGE_2 and PGE_3—is not 'naturally occurring.' Those compounds, as far as the record establishes, do not exist in nature in pure form, and appellants have neither merely discovered, nor claimed sufficiently broadly to encompass, what has previously existed in fact in nature's storehouse, albeit unknown, or what has previously been known to exist." *Id.* at 1401, 166 USPQ at 261–62. Like other chemical compounds, DNA molecules are eligible for patents when isolated from their natural state and purified or when synthesized in a laboratory from chemical starting materials.

A patent on a gene covers the isolated and purified gene but does not cover the gene as it occurs in nature. Thus, the concern that a person whose body "includes" a patented gene could infringe the patent is misfounded. The body does not contain the patented, isolated and purified gene because genes in the body are not in the patented, isolated and purified form. When the patent issued for purified adrenaline about one hundred years ago, people did not infringe the patent merely because their bodies naturally included unpurified adrenaline.

(3) *Comment:* Several comments suggested that the USPTO should seek guidance from Congress as to whether naturally occurring genetic sequences are patentable subject matter. *Response:* The suggestion is not adopted. Congress adopted the current statute defining patentable subject matter (35 U.S.C. 101) in 1952. The legislative history indicates that Congress intended "anything under the sun that is made by man" to be eligible for patenting. S. Rep. No. 1979, 82d Cong., 2d Sess., 5 (1952); H.R. Rep. No. 1923, 82d Cong., 2d Sess., 6 (1952). The Supreme Court interprets the statute to cover a "nonnaturally occurring manufacture or composition of matter—a product of human ingenuity." *Diamond* v. *Chakrabarty*, 447 U.S. 303, 309, 206 USPQ 193, 197 (1980). Thus, the intent of Congress with regard to patent eligibility for chemical compounds has already been determined: DNA compounds having naturally occurring sequences are eligible for patenting when isolated from their natural state and purified, and when the application meets the statutory criteria for patentability. The genetic sequence data represented by strings of the letters A, T, C and G alone is raw, fundamental sequence data, i.e., nonfunctional descriptive information. While descriptive sequence information alone is not patentable subject matter, a new and useful purified and isolated DNA compound described by the sequence is eligible for patenting, subject to satisfying the other criteria for patentability.

(4) *Comment:* Several comments state that patents should not issue for genes because the sequence of the human genome is at the core of what it means to be human and no person should be able to own/control something so basic. Other comments stated that patents should be for marketable inventions and not for discoveries in nature. *Response:* The comments are not adopted. Patents do not confer ownership of genes, genetic information, or sequences. The patent system promotes progress by securing a complete disclosure of an invention to the public, in exchange for the inventor's legal right to exclude other people from making, using, offering for sale, selling, or importing

the composition for a limited time. That is, a patent owner can stop infringing activity by others for a limited time.

Discoveries from nature have led to marketable inventions in the past, but assessing the marketability of an invention is not pertinent to determining if an invention has a specific, substantial, and credible use. "[D]evelopment of a product to the extent that it is presently commercially salable in the marketplace is not required to establish 'usefulness' within the meaning of § 101." *In re Langer,* 503 F.2d 1380, 1393, 183 USPQ 288, 298 (CCPA 1974). Inventors are entitled to patents when they have met the statutory requirements for novelty, nonobviousness and usefulness, and their patent disclosure adequately describes the invention and clearly teaches others how to make and use the invention. The utility requirement, as explained by the courts, only requires that the inventor disclose a practical or real world benefit available from the invention, i.e., a specific, substantial and credible utility. As noted in a response to other comments, it is a long tradition in the United States that discoveries from nature which are transformed into new and useful products are eligible for patents.

(5) *Comment:* Several comments state that the Guidelines mean that anyone who discovers a gene will be allowed a broad patent covering any number of possible applications even though those uses may be unattainable and unproven. Therefore, according to these comments, gene patents should not be issued. *Response:* The comment is not adopted. When a patent claiming a new chemical compound issues, the patentee has the right to exclude others from making, using, offering for sale, selling, or importing the compound for a limited time. The patentee is required to disclose only one utility, that is, teach others how to use the invention in at least one way. The patentee is not required to disclose all possible uses, but promoting the subsequent discovery of other uses is one of the benefits of the patent system. When patents for genes are treated the same as for other chemicals, progress is promoted because the original inventor has the possibility to recoup research costs, because others are motivated to invent around the original patent, and because a new chemical is made available as a basis for future research. Other inventors who develop new and nonobvious methods of using the patented compound have the opportunity to patent those methods.

(6) *Comment:* One comment suggests that the USPTO should not allow the patenting of ESTs because it is contrary to indigenous law, because the Supreme Court's *Diamond* v. *Chakrabarty* decision was a bare 5-to-4 decision, because it would violate the Thirteenth Amendment of the U.S. Constitution, because it violates the novelty requirement of the patent laws, because it will exacerbate tensions between indigenous peoples and western academic/research communities and because it will undermine indigenous peoples' own research and academic institutions. The comment urges the USPTO to institute a moratorium on patenting of life forms and natural processes. *Response:* The comments are not adopted. Patents on chemical compounds such as ESTs do not implicate the Thirteenth Amendment. The USPTO must administer the patent statutes as the Supreme Court interprets them. When Congress enacted § 101, it indicated that "anything under the sun that is made by man" is subject matter for a patent. S. Rep. No. 1979, 82d Cong., 2d Sess., 5 (1952); H.R. Rep. No. 1923, 82d Cong., 2d Sess., 6 (1952). The Supreme Court has interpreted § 101 many times without overturning it. *See, e.g., Diamond* v. *Diehr,* 450 U.S. 175, 209 USPQ 1 (1981) (discussing cases construing section 101). Under United States law, a patent applicant is entitled to a patent when an invention meets the patentability criteria of title 35. Thus, ESTs which meet the criteria for utility, novelty, and nonobviousness are eligible for patenting when the application teaches those of skill in the art how to make and use the invention.

(7) *Comment:* Several comments state that patents should not issue for genes because patents on genes are delaying medical research and thus there is no societal benefit associated with gene patents. Others state that granting patents on genes at any stage of research deprives others of incentives and the ability to continue exploratory research and development. Some comment that patentees will deny access to genes and our property (our genes) will be owned by others. *Response:* The comments are not adopted. The incentive to make discoveries and inventions is generally spurred, not inhibited, by patents. The disclosure of genetic inventions provides new opportunities for further development. The patent statutes provide that a patent must be granted when at least one specific, substantial and credible utility has been disclosed, and the application satisfies the other statutory requirements. As long as one specific, substantial and credible use is disclosed and the statutory requirements are met, the USPTO is not authorized to withhold the patent until another, or better, use is discovered. Other researchers may discover higher, better or more practical uses, but they are advantaged by the starting point that the original disclosure provides. A patent grants exclusionary rights over a patented composition but does not grant ownership of the composition. Patents are not issued on compositions in the natural environment but rather on isolated and purified compositions.

(8) *Comment:* Several comments stated that DNA should be considered unpatentable because a DNA sequence by itself has little utility. *Response:* A DNA sequence—*i.e.,* the sequence of base pairs making up a DNA molecule—is simply one of the properties of a DNA molecule. Like any descriptive property, a DNA sequence itself is not patentable. A purified DNA *molecule* isolated from its natural environment, on the other hand, is a chemical compound and is patentable if all the statutory requirements are met. An isolated and purified DNA molecule may meet the statutory utility requirement if, *e.g.,* it can be used to produce a useful protein or it hybridizes near and serves as a marker for a disease gene. Therefore, a DNA molecule is not *per se* unpatentable for lack of utility, and each application claim must be examined on its own facts.

(9) *Comment:* One comment states that the disclosure of a DNA sequence has inherent value and that possible uses for the DNA appear endless, even if no single use has been worked out. According to the comment, the "basic social contract of the patent deal" requires that such a discovery should be patentable, and that patenting should be "value-blind." *Response:* The comment is not adopted. The Supreme Court did not find a similar argument persuasive in *Brenner* v. *Manson,* 383 U.S. 519 (1966). The courts interpret the statutory term "useful" to require disclosure of at least one available practical benefit to the public. The Guidelines reflect this determination by requiring the disclosure of at least one specific, substantial, and credible utility. If no such utility is disclosed or readily apparent from an application, the Office should reject the claim. The applicant may rebut the Office position by showing that the invention does have a specific, substantial, and credible utility that would have been recognized by one of skill in the art at the time the application was filed.

(10) *Comment:* Several comments stated that the scope of patent claims directed to DNA should be limited to applications or methods of using DNA, and should not be allowed to

encompass the DNA itself. *Response:* The comment is not adopted. Patentable subject matter includes both "process[es]" and "composition[s] of matter." 35 U.S.C. 101. Patent law provides no basis for treating DNA differently from other chemical compounds that are compositions of matter. If a patent application claims a composition of matter comprising DNA, and the claims meet all the statutory requirements of patentability, there is no legal basis for rejecting the application.

(11) *Comment:* Several comments stated that DNA patent claim scope should be limited to uses that are disclosed in the patent application and that allowing patent claims that encompass DNA itself would enable the inventor to assert claims to "speculative" uses of the DNA that were not foreseen at the time the patent application was filed. *Response:* The comment is not adopted. A patent on a composition gives *exclusive* rights to the composition for a limited time, even if the inventor disclosed only a single use for the composition. Thus, a patent granted on an isolated and purified DNA composition confers the right to exclude others from *any* method of using that DNA composition, for up to 20 years from the filing date. This result flows from the language of the statute itself. When the utility requirement and other requirements are satisfied by the application, a patent granted provides a patentee with the right to exclude others from, *inter alia,* "using" the patented composition of matter. *See* 35 U.S.C. 154. Where a new use is discovered for a patented DNA composition, that new use may qualify for its own process patent, notwithstanding that the DNA composition itself is patented.

By statute, a patent is required to disclose one practical utility. If a well-established utility is readily apparent, the disclosure is deemed to be implicit. If an application fails to disclose one specific, substantial, and credible utility, and the examiner discerns no well-established utility, the examiner will reject the claim under section 101. The rejection shifts the burden to the applicant to show that the examiner erred, or that a well-established utility would have been readily apparent to one of skill in the art. The applicant cannot rebut the rejection by relying on a utility that would not have been readily apparent at the time the application was filed. *See, e.g., In re Wright,* 999 F.2d 1557, 1562–63, 27 USPQ2d 1510, 1514 (Fed. Cir. 1993) ("developments occurring after the filing date of an application are of no significance regarding what one skilled in the art believed as of the filing date").

(12) *Comment:* Several comments stated that DNA should be freely available for research. Some of these comments suggested that patents are not necessary to encourage additional discovery and sequencing of genes. Some comments suggested that patenting of DNA inhibits biomedical research by allowing a single person or company to control use of the claimed DNA. Another comment expressed concern that patenting ESTs will impede complete characterization of genes and delay or restrict exploration of genetic materials for the public good. *Response:* The scope of subject matter that is eligible for a patent, the requirements that must be met in order to be granted a patent, and the legal rights that are conveyed by an issued patent, are all controlled by statutes which the USPTO must administer. "Whoever invents or discovers any new and useful * * * composition of matter * * * may obtain a patent therefor." 35 U.S.C. 101. Congress creates the law and the Federal judiciary interprets the law. The USPTO must administer the laws as Congress has enacted them and as the Federal courts have interpreted them. Current law provides that when the statutory patentability requirements are met, there is no basis to deny patent applications claiming DNA compositions, or to limit a patent's scope in order to allow free access to the use of the invention during the patent term.

(13) *Comment:* Several comments suggested that DNA sequences should be considered unpatentable because sequencing DNA has become so routine that determining the sequence of a DNA molecule is not inventive. *Response:* The comments are not adopted. A DNA sequence is not patentable because a sequence is merely descriptive information about a molecule. An isolated and purified DNA molecule may be patentable because a molecule is a "composition of matter," one of the four classes of invention authorized by 35 U.S.C. 101. A DNA molecule must be *nonobvious* in order to be patentable. Obviousness does not depend on the amount of work required to characterize the DNA molecule. *See* 35 U.S.C. 103(a) ("Patentability shall not be negatived by the manner in which the invention was made."). As the nonobviousness requirement has been interpreted by the U.S. Court of Appeals for the Federal Circuit, whether a claimed DNA molecule would have been obvious depends on whether a molecule having the particular *structure* of the DNA would have been obvious to one of ordinary skill in the art at the time the invention was made. *See, e.g., In re Deuel,* 51 F.3d 1552, 1559, 34 USPQ2d 1210, 1215 (Fed. Cir. 1995) ("[T]he existence of a general method of isolating cDNA or DNA molecules is essentially irrelevant to the question whether the specific molecules themselves would have been obvious."); *see also, In re Bell,* 991 F.2d 781, 26 USPQ2d 1529 (Fed. Cir. 1993).

(14) *Comment:* One comment suggested that genes ought to be patentable only when the complete sequence of the gene is disclosed and a function for the gene product has been determined. *Response:* The suggestion is not adopted. To obtain a patent on a chemical compound such as DNA, a patent applicant must adequately describe the compound and must disclose how to make and use the compound. 35 U.S.C. 101, 112. "An adequate written description of a DNA * * * requires a precise definition, *such as* by structure, formula, chemical name, or physical properties." *Univ. of California* v. *Eli Lilly & Co.,* 119 F.3d 1559, 1556, 43 USPQ2d 1398, 1404 (Fed. Cir. 1997) (emphasis added, internal quote omitted). Thus, describing the complete chemical structure, *i.e.,* the DNA sequence, is one method of describing a DNA molecule but it is not the only method. In addition, the utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have a specific and substantial utility because, *e.g.,* it hybridizes near a disease-associated gene or it has a gene-regulating activity.

(15) *Comment:* One comment stated that the specification should "disclose the invention," including why the invention works and how it was developed. *Response:* The comment is not adopted. The comment is directed more to the requirements imposed by 35 U.S.C. 112 than to those of 35 U.S.C. 101. To satisfy the enablement requirement of 35 U.S.C. 112, ¶ 1, an application must disclose the claimed invention in sufficient detail to enable a person of ordinary skill in the art to make and use the claimed invention. To satisfy the written description requirement of 35 U.S.C. 112, ¶ 1, the description must show that the applicant was in possession of the claimed invention at the time of filing. If all the requirements under 35 U.S.C. 112, ¶1, are met, there is no statutory basis to require disclosure of why an invention works or how it was developed. "[I]t is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works." *Newman* v. *Quigg,*

877 F.2d 1575, 1581, 11 USPQ2d 1340, 1345 (Fed. Cir. 1989).

(16) *Comment:* One comment suggested that patents should "allow for others to learn from and improve the invention." The comment suggested that claims to patented plant varieties should not prohibit others from using the patented plants to develop improved varieties. The comment also stated that uses of plants in speculative manners should not be permitted. *Response:* By statute, a patent provides the patentee with the right to exclude others from, *inter alia,* making and using the claimed invention, although a limited research exemption exists. *See* 35 U.S.C. 163, 271(a), (e). These statutory provisions are not subject to revision by the USPTO and are not affected by these Guidelines. Where a plant is claimed in a utility patent application, compliance with the statutory requirements for utility under 35 U.S.C. 101 only requires that a claimed invention be supported by at least one specific, substantial and credible utility. It is somewhat rare for academic researchers to be sued by commercial patent owners for patent infringement. Most inventions are made available to academic researchers on very favorable licensing terms, which enable them to continue their research.

(17) *Comment:* Two comments suggested that although the USPTO has made a step in the right direction in raising the bar in the Utility Guidelines, there is still a need to apply stricter standards for utility. *Response:* The USPTO is bound by 35 U.S.C. 101 and the case law interpreting § 101. The Guidelines reflect the USPTO's understanding of § 101.

(18) *Comment:* Several comments addressed specific concerns about the examiner training materials. *Response:* The comments received with respect to the training materials will be taken under advisement as the Office revises the training materials. Except for comments with regard to whether sequence homology is sufficient to demonstrate a specific and substantial credible utility, specific concerns about the training materials will not be addressed herein as they will not impact the language of the guidelines.

(19) *Comment:* Several comments suggested that the use of computer-based analysis of nucleic acids to assign a function to a given nucleic acid based upon homology to prior art nucleic acids found in databases is highly unpredictable and cannot form a basis for an assignment of function to a putatively encoded protein. These comments also indicate that even in instances where a general functional assignment may be reasonable, the assignment does not provide information regarding the actual biological activity of an encoded protein and therefore patent claims drawn to such nucleic acids should be limited to method of use claims that are explicitly supported by the as-filed specification(s). These comments also state that if homology-based utilities are acceptable, then the nucleic acids, and proteins encoded thereby, should be considered as obvious over the prior art nucleic acids. On the other hand, one comment stated that homology is a standard, art-accepted basis for predicting utility, while another comment stated that any level of homology to a protein with known utility should be accepted as indicative of utility. *Response:* The suggestions to adopt a *per se* rule rejecting homology-based assertions of utility are not adopted. An applicant is entitled to a patent to the subject matter claimed unless statutory requirements are not met (35 U.S.C. 101, 102, 103, 112). When the USPTO denies a patent, the Office must set forth at least a *prima facie* case as to why an applicant has not met the statutory requirements. The inquiries involved in assessing utility are fact dependent, and the determinations must be made on the basis of scientific evidence. Reliance on the commenters' *per se* rule, rather than a fact dependent inquiry, is impermissible because the commenters provide no scientific evidence that homology-based assertions of utility are inherently unbelievable or involve implausible scientific principles. *See, e.g., In re Brana,* 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (rejection of claims improper where claims did "not suggest an inherently unbelievable undertaking or involve implausible scientific principles' and where "prior art * * * discloses structurally similar compounds to those claimed by the applicants which have been proven * * * to be effective").

A patent examiner must accept a utility asserted by an applicant unless the Office has evidence or sound scientific reasoning to rebut the assertion. The examiner's decision must be supported by a preponderance of all the evidence of record. *In re Oetiker,* 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). More specifically, when a patent application claiming a nucleic acid asserts a specific, substantial, and credible utility, and bases the assertion upon homology to existing nucleic acids or proteins having an accepted utility, the asserted utility must be accepted by the examiner unless the Office has sufficient evidence or sound scientific reasoning to rebut such an assertion. "[A] 'rigorous correlation' need not be shown in order to establish practical utility; 'reasonable correlation' is sufficient." *Fujikawa* v. *Wattanasin,* 93 F.3d 1559, 1565, 39 USPQ2d 1895, 1900 (Fed. Cir. 1996). The Office will take into account both the nature and degree of the homology.

When a class of proteins is defined such that the members share a specific, substantial, and credible utility, the reasonable assignment of a new protein to the class of sufficiently conserved proteins would impute the same specific, substantial, and credible utility to the assigned protein. If the preponderance of the evidence of record, or of sound scientific reasoning, casts doubt upon such an asserted utility, the examiner should reject the claim for lack of utility under 35 U.S.C. 101. For example, where a class of proteins is defined by common structural features, but evidence shows that the members of the class do not share a specific, substantial functional attribute or utility, despite having structural features in common, membership in the class may not impute a specific, substantial, and credible utility to a new member of the class. When there is a reason to doubt the functional protein assignment, the utility examination may turn to whether or not the asserted protein encoded by a claimed nucleic acid has a well-established use. If there is a well-established utility for the protein and the claimed nucleic acid, the claim would meet the requirements for utility under 35 U.S.C. 101. If not, the burden shifts to the applicant to provide evidence supporting a well-established utility. There is no *per se* rule regarding homology, and each application must be judged on its own merits.

The comment indicating that if a homology-based utility could meet the requirements set forth under 35 U.S.C. 101, then the invention would have been obvious, is not adopted. Assessing nonobviousness under 35 U.S.C. 103 is separate from analyzing the utility requirements under 35 U.S.C. 101. When a claim to a nucleic acid supported by a homology-based utility meets the utility requirement of section 101, it does not follow that the claimed nucleic acid would have been *prima facie* obvious over the nucleic acids to which it is homologous. "[S]ection 103 requires a fact-intensive comparison of the [claim] with the prior art rather than the mechanical application of one or another *per se* rule." *In re Ochiai,* 71 F.3d 1565, 1571, 37 USPQ2d 1127, 1132 (Fed. Cir. 1995). Nonobviousness must be determined according to the analysis

in *Graham* v. *John Deere*, 383 U.S. 1, 148 USPQ 459 (1966). *See also, In re Dillon*, 919 F.2d 688, 692, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990) (in banc) ("structural similarity between claimed and prior art subject matter, * * * *where the prior art gives reason or motivation to make the claimed compositions*, creates a prima facie case of obviousness") (emphasis added). Where "the prior art teaches a specific, structurally-definable compound [] the question becomes whether the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention." *In re Deuel*, 51 F.3d 1552, 1558, 34 USPQ2d 1210, 1214 (Fed. Cir. 1995).

(20) *Comment:* Several comments indicated that in situations where a well-established utility is relied upon for compliance with 35 U.S.C. 101, the record should reflect what that utility is. One comment stated that the record should reflect whether the examiner accepted an asserted utility or relied upon a well-established utility after dismissing all asserted utilities. Another comment stated that when the examiner relies on a well-established utility not explicitly asserted by the applicant, the written record should clearly identify this utility and the rationale for considering it specific and substantial. *Response:* The comments are not adopted. Only one specific, substantial and credible utility is required to satisfy the statutory requirement. Where one or more well-established utilities would have been readily apparent to those of skill in the art at the time of the invention, an applicant may rely on any one of those utilities without prejudice. The record of any issued patent typically reflects consideration of a number of references in the prior art that the applicant or the examiner considered material to the claimed invention. These references often indicate uses for related inventions, and any patents listed typically disclose utilities for related inventions. Thus, even when the examiner does not identify a well-established utility, the record as a whole will likely disclose readily apparent utilities. Just as the examiner without comment may accept a properly asserted utility, there is no need for an examiner to comment on the existence of a well-established utility. However, the Guidelines have been revised to clarify that a well-established utility is a specific, substantial, and credible utility that must be readily apparent to one skilled in the art. Most often, the closest prior art cited and applied in the course of examining the application will demonstrate a well-established utility for the invention.

(21) *Comment:* Several comments stated that the Guidelines erroneously burden the examiner with proving that a person of skill in the art would not be aware of a well-established utility. One comment states that this requires the examiner to prove a negative. Another comment states that the Guidelines should direct examiners that if a specific utility has not been disclosed, the applicant should be required to identify a specific utility. *Response:* The comments have been adopted in part. The Guidelines have been revised to indicate that where the applicant has not asserted a specific, substantial, and credible utility, and the examiner does not perceive a well-established utility, a rejection under § 101 should be entered. That is, if a well-established utility is not readily apparent and an invention is not otherwise supported by an asserted specific, substantial, and credible utility, the burden will be shifted to applicant to show either that the specification discloses an adequate utility, or to show that a well-established utility exists for the claimed invention. Again, most often the search of the closest prior art will reveal whether there is a well-established utility for the claimed invention.

(22) *Comment:* Several comments suggested that further clarification was required with regard to the examiner's determination that there is an adequate nexus between a showing supporting a well-established utility and the application as filed. The comments indicated that the meaning of this "nexus" was unclear. *Response:* The Guidelines have been modified to reflect that evidence provided by an applicant is to be analyzed with regard to a concordance between the showing and the full scope and content of the claimed invention as disclosed in the application as filed. In situations where the showing provides adequate evidence that the claim is supported by at least one asserted specific, substantial, and credible or well-established utility, the rejections under 35 U.S.C. 101 and 112, first paragraph, will be withdrawn. However, the examiner is instructed to consider whether or not the specification, in light of applicant's showing, is enabled for the use of the full scope of the claimed invention. Many times prior patents and printed publications provided by applicant will clearly demonstrate that a well-established utility exists.

(23) *Comment:* One comment states that the Office is using an improper standard in assessing "specific" utility. According to the comment, a distinction between "specific" and "general" utilities is an overreaching interpretation of the specificity requirement in the case law because "unique" or "particular" utilities have never been required by the law. The comment states that the specificity requirement concerns sufficiency of disclosure, *i.e.*, teaching how to make and use a claimed invention, not the utility requirement. The comment states that the specificity requirement is to be distinguished from the "substantial" utility requirement, and that the *Brenner* v. *Manson* decision concerned only a "substantial" utility issue, not specificity. *Response:* The comment is not adopted. The disclosure of only a general utility rather than a particular utility is insufficient to meet statutory requirements. Although the specificity requirement is relevant to § 112, it is not severable from the utility requirement.

> [S]urely Congress intended § 112 to presuppose *full satisfaction* of the requirements of § 101. Necessarily, compliance with § 112 requires a description of how to use presently useful inventions, otherwise an applicant would anomalously be required to teach how to use a useless invention. As this court stated in *Diederich*, quoting with approval from the decision of the board:
>
> 'We do not believe that it was the intention of the statutes to require the Patent Office, the courts, or the public to play the sort of guessing game that might be involved if an applicant could satisfy the requirements of the statutes by indicating the usefulness of a claimed compound in terms of possible use so general as to be meaningless and then, after his research or that of his competitors has definitely ascertained an actual use for the compound, adducing evidence intended to show that a particular specific use would have been obvious to men skilled in the particular art to which this use relates.' As the Supreme Court said in Brenner v. Manson:
>
> '* * * a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.'
>
> *In re Kirk*, 376 F.2d 936, 942, 153 USPQ 48, 53 (CCPA 1967) (affirming rejections under §§ 101 and 112) (emphasis in original).

II. Guidelines for Examination of Applications for Compliance With the Utility Requirement

A. Introduction

The following Guidelines establish the policies and procedures to be followed by Office personnel in the evaluation of any patent application for compliance with the utility requirements of 35 U.S.C. 101 and 112. These Guidelines have been promulgated to assist Office personnel in their review of applications for compliance with the utility

SYNTHETIC COMMUNICATIONS, 31(1), 1–7 (2001)

QUATERNARY AMMONIUM SALT-ASSISTED ORGANIC REACTIONS IN WATER: ALKYLATION OF PHENOLS

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ABSTRACT

A series of quaternary ammonium salts has been tested as phase transfer agents to promote reactions between phenols and alkyl halides in an aqueous solution of sodium hydroxide in the absence of organic solvent. Methyltrioctylammonium chloride emerges as the most effective catalyst.

Nowadays, there is an increasing awareness of the urgent necessity to limit, as far as possible, any source of pollution. Consequently and in response to the public pressure, the environmental legislation is becoming ever more severe. Facing up to those facts, chemists have to dedicate numerous efforts to the development of clean technologies.

That new challenge has led recently to a growing interest in the displacement of organic reactions to aqueous media (1–3), which has been achieved successfully in the Ruhr Chemie Rhône-Poulenc hydroformylation process (4).

Water is an abundant, cheap, nontoxic, and nondangerous solvent. Obviously, it does not dissolve most of the organic reactants, but that fact has been recognized

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as a benefit on rates and selectivities of several transformations (1–3). Moreover, the addition of a phase transfer agent, generally a quaternary ammonium salt, enables to improve an intimate contact with an organic layer (3–11).

The aim of this paper is to disclose suitable experimental conditions to promote alkylation of phenols in an aqueous solution of sodium hydroxide and in the absence of any organic solvent. That reaction yields aryl ethers, a functionality that is a key constituent in the structures of many pharmaceutically important chemicals.

RESULTS

The reaction between phenols and alkyl halides in an aqueous solution of sodium hydroxide requires the contact between two nonmiscible phases and yields a water-insoluble product. Therefore, its course can be monitored readily by UV spectroscopy on samples of the aqueous phase, as the phenolates are the sole species that absorb in that wavelength region. That method was used to select the most attractive phase transfer catalyst from a kinetic point of view in a model reaction involving 1,2-dihydroxybenzene (**1a**-Fig. 1; $\epsilon = 2870$ l mol^{-1} cm^{-1}; λ max $= 275$ nm) and iodomethane. By that way, we observed that **1a** reacts slowly with an excess (3 eq) of iodomethane in an aqueous solution of sodium hydroxide (5M) at 50°C.

After 1 h, only 5% of the starting material **1a** is consumed. Addition of a quaternary ammonium salt (10% mol relative to **1a**) accelerates the process as indicated by inspection of the results collected in Table 1. Among the transfer agents we tested, methyltrioctylammonium chloride (Aliquat® 336) emerges as the most effective catalyst. Interestingly, in contrast with conclusions (12) dealing with other phase transfer catalysis experiments, no synergistic effect of a crown ether-quaternary ion salt pair takes place.

To evaluate the synthetic potential of the method, we performed the same experiments in a boiling solution of sodium hydroxide, extending the reaction time arbitrarily to 1 h. After cooling, the mixture was extracted with dichloromethane. Before evaporation of the solvent, the organic layer was filtered through a cake of alumina to retain the ammonium salt. Yields in 1,2-dimethoxybenzene, determined by ^{1}H NMR, are collected in Table 1. The data parallel the results of the

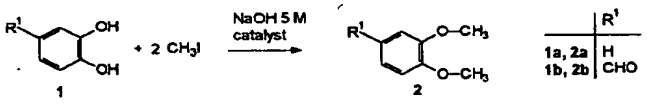

Figure 1.

Table 1. Influence of the Catalyst on the Alkylation of **1a** with Methyl Iodide

Catalyst (10% mol relative to **1a**)	[1a] (mol/l)[a] after 30 mn	60 mn	Isolated Yield[b], %
None	0.78	0.76	25
Benzyltriethylammonium chloride	0.68	0.56	40
Tetrabutylammonium hydrogenosulfate (TBA)	0.44	0.38	65
TBA/15-crown-5	0.54	0.51	60
Cetyltrimethylammonium bromide	0.45	0.35	80
Methyltrioctylammonium chloride	0.45	0.33	90

[a] C_0 (**1a**) = 0.8 mol l^{-1}; C_0 (CH_3I) = 2.4 mol l^{-1}; T = 50°C.
[b] C_0 (**1a**) = 0.8 mol l^{-1}; C_0 (CH_3I) = 1.6 mol l^{-1}; T = reflux; time = 1 hour.

kinetic study. Indeed, the highest yield in isolated product was obtained by using methyltrioctylammonium chloride as the transfer agent. Cetyltrimethylammonium bromide is also efficient, but its tendancy to foam complicates the experimental procedure. The other salts give lower yields so we did not use them. Experimentally, we also noticed that the stoechiometric amount of iodomethane is sufficient to effect the dialkylation. In agreement with the mechanism of the reaction, which requires the formation of phenolate anions, a lower concentration of NaOH (0.5 M) or the use of sodium hydrogenocarbonate (5 M, 0.5 M) as the base (in the presence of 10% mol of methyltriocylammonium) dramatically decreases the yield in 1,2-dimethoxybenzene to 30, 20, or 5%, respectively. In that sense, too, sodium dodecylsulfate (10% mol), a popular anionic surfactant, exhibits a poor but positive activity (35%).

Having a simple procedure to methylate 1,2-dihydroxybenzene, we wished to estimate its range of applicability. Under our experimental conditions, compound

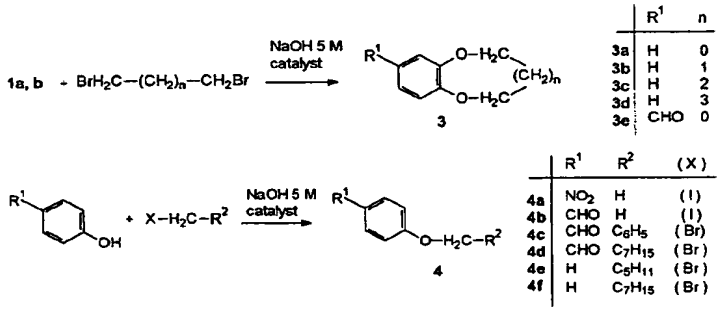

Figure 2.

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Table 2. Results for the Alkylation of **1a**, **1b**, and Various Phenols in the Presence of Methyltrioctylammonium Chloride

Product	Isolated Yield, %	Lit. Ref.
2a	90	21–24
2b	55	23–26
3a	60	23, 24, 27, 28
3b	65	14, 29
3c	75	14, 30
3d	95	14, 29
3e	50	23, 24, 31
4a	90	23, 24, 32, 33
4b	90	23, 24, 34, 35
4c	55	23, 24, 36, 37
4d	65	38
4e	95	39–41
4f	70	42–44

1a readily reacts with 1,2-dibromoethane, 1,3-dibromopropane, 1,4-dibromobutane, and even 1,5-dibromopentane. Yields vary from 50 to 95%. In particular, derivative **3c** has been obtained in 75% yield, whereas Ziegler (7) reports that its preparation requires two steps and that the yield of the second step does not exceed 40%. 3,4-Dihydroxybenzaldehyde (**1b**) and other phenols also can be alkylated under our experimental conditions, as indicated by the examples presented in Figure 2 (isolated yields are reported in Table 2). Mention should be made that in all cases the crude final products were isolated by decantation or filtration, thus limiting the use of an organic solvent to the purification by recrystallization when the expected compound is a solid.

CONCLUSION

Elegant protocols for the preparation of aryl ethers have recently been published. They recommend the use of polymer-supported bases (15) or irradiation of dry media with microwaves (16,17). This paper presents another simple experimental procedure (that could readily be scaled up) to alkylate phenols in an aqueous basic solution in the presence of a catalytic amount of methyltrioctylammonium and in the absence of any organic solvent. It is characterized by its wide range of applicability as it enables, e.g., the formation of 6- to 9-membered benzo fused systems, as well as the use of long chain alkyl halides. Our experimental conditions largely differ from those described by Bashall and Collins (18) as the

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ammonium salt does not play the role of a solvent. Let us also emphasize that we did not observe any poisoneous effect of the iodide ion when alkyl iodides were involved (18, 19), and that by-products from a Cannizzaro reaction (20) were not detected when starting from hydroxybenzaldehydes.

EXPERIMENTAL SECTION

All reagents, catalysts, and solvents are commercially available (Aldrich, Acros Organics). All products (**2**, **3**, **4**) have been described in the literaure and were fully characterized by their melting point (hot-stage microscope) or boiling point, and by their spectral data (NMR: Varian EM 360-L, Bruker AMX; IR: Perkin-Elmer 1760K).

Quantitative Study

A stirred mixture of 1,2-dihydroxybenzene (5.51 g; 50 mmol) and a catalyst (see Table 1; 5 mmol) in a 5 M aqueous solution (62.50 mL) of sodium hydroxide was held under thermostatic control at 50°C for two hours. Iodomethane (9.34 mL; 150 mmol) was added. A sample of the mixture was taken every 10 minutes, rapidly cooled down to 0°C, and diluted (2000 X) for UV analysis (Varian Cary 118).

General Procedure for the Alkylation

A mixture of the phenol (100 mmol), the alkyl halide (one or two equivalents), and methyltrioctylammonium chloride (10 mmol) in a 5 M aqueous solution (100 mL) of sodium hydroxide was stirred and heated under reflux for one hour. After cooling, the crude product was separated (decantation or filtration) and purified by distillation or recrystallization.

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Photolysis of the Ozonide Derived from 1,4-Benzodioxins. Synthesis of Labile *o*-Benzoquinones[1]

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By the photolysis of the ozonide derived from 1,4-benzodioxins, *o*-benzoquinones were obtained in moderate yields independent of the stability of *o*-benzoquinones and of the substituent groups, except the nitro group. Through the mechanistic studies, it was indicated that *o*-benzoquinones were formed through a radical decomposition pathway, while catechols were formed through an ionic decomposition pathway induced by acidic impurities.

Many inorganic salts are widely used as oxidants for the synthesis of *o*-benzoquinones.[2] However, since oxidation with inorganic oxidants requires severe reaction conditions, many *o*-benzoquinones have never been synthesized owing to their high reactivity toward decomposition and polymerization. Therefore, a new methodology under mild conditions was required for the synthesis of labile *o*-benzoquinones.

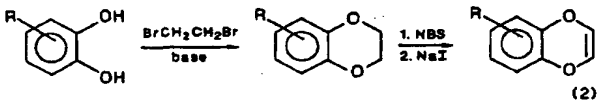
In 1968, Story et al. reported that a unique oxidative decomposition reaction proceeded through the ozonolysis of 2,5-dimethyl-3-hexene (1) followed by photolysis. When ozonide 2 was irradiated, a homolysis of the oxygen–oxygen bond followed by a double β-scission occurred to give formic anhydride and 2,3-dimethylbutane (3), which was formed by coupling of the resulting radical pair (Scheme I).[3] This reaction is characterized by the following features. First, since the substrate is oxidized by the gaseous oxidant (ozone), no complex workup procedures such as extraction are necessary for isolation of the product. Second, because the reaction consists of two independent stages, namely the oxidation stage (formation of an ozonide) and the decomposition stage, contact of the final product with the oxidant can be avoided. Third, photolysis of ozonides can be carried out under a nonaqueous condition at low temperature. These features enable the synthesis of labile compounds such as Dewar benzene[4] and cyclobutadiene[5] derivatives. Even more labile compounds such as aziridine-2,3-dione, which readily decomposes to isocyanate and carbon monoxide at −78 °C, can be synthesized by the application of this reaction to maleimide.[6]

Application of this reaction to the double bond at the 2-position of 1,4-benzodioxins should yield a diradical 4, which is a canonical form of *o*-benzoquinones (eq 1). Therefore, this reaction is expected to be a good method for the synthesis of labile *o*-benzoquinones. Here we report the results of the syntheses of *o*-benzoquinones by photolysis of ozonides derived from ozonolysis of 1,4-benzodioxins 5.

4 (1)

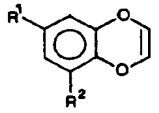
Results and Discussion

1,4-Benzodioxins 5 were prepared from the corresponding catechols 6. In the literature, the synthesis of 1,4-benzodioxins was reported as shown in eq 2.

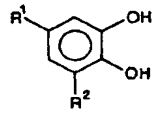


(2)

According to this method, 3,5-di-*tert*-butylcatechol (6d) was treated with 1,2-dibromoethane in dichloromethane in the presence of aqueous sodium hydroxide and a phase-transfer catalyst. However, the desired 1,4-benzodioxan was obtained only in an unsatisfactory yield, and 1,3-benzodioxolane derivative 8 was obtained as a main product. This undesired product seemed to be formed by the reaction of the catechol 6d with the solvent, dichloromethane. The synthesis of 1,4-benzodioxans was accomplished successfully by using potassium carbonate in ethylene glycol.[8] 1,4-Benzodioxans were oxidized by *N*-bromosuccinimide, and 1,4-benzodioxins were obtained subsequently.



5a: $R^1 = R^2 = H$
b: $R^1 = t\text{-Bu}$, $R^2 = H$
c: $R^1 = Cl$, $R^2 = H$
d: $R^1 = R^2 = t\text{-Bu}$
e: $R^1 = NO_2$, $R^2 = H$
f: $R^1 = PhCO$, $R^2 = H$



6a: $R^1 = R^2 = H$
b: $R^1 = t\text{-Bu}$, $R^2 = H$
c: $R^1 = Cl$, $R^2 = H$
d: $R^1 = R^2 = t\text{-Bu}$
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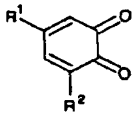
f: $R^1 = PhCO$, $R^2 = H$



7a: $R^1 = R^2 = H$
b: $R^1 = t\text{-Bu}$, $R^2 = H$
c: $R^1 = Cl$, $R^2 = H$
d: $R^1 = R^2 = t\text{-Bu}$
e: $R^1 = NO_2$, $R^2 = H$

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(2) Thomson, R. H., In *The Chemistry of the Quinoid Compounds*; Patai, S., Ed.; Wiley: London, 1974; Vol. 1.
(3) Story, P. R.; Morrison, W. H., III; Hall, T. K.; Farine, J.-C.; Bishop, C. E. *Tetrahedron* **1968**, *24*, 3291.
(4) (a) Criegee, R. *Chimia* **1968**, *22*, 392. (b) Carty, D. T. *Tetrahedron Lett.* **1969**, 4753.
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(7) (a) Coudert, G.; Guillaumet, G.; Loubinoux, B. *Tetrahedron Lett.* **1978**, 1069. (b) Guillaumet, G.; Coudert, G.; Loubinoux, B. *Ibid.* **1979**, 4379.
(8) Heertjes, P. M.; Knope, A. A.; Talsma. H.; Andriesse, P. *J. Chem. Soc.* **1954**, 18.

0022-3263/87/1952-5616$01.50/0

Scheme I

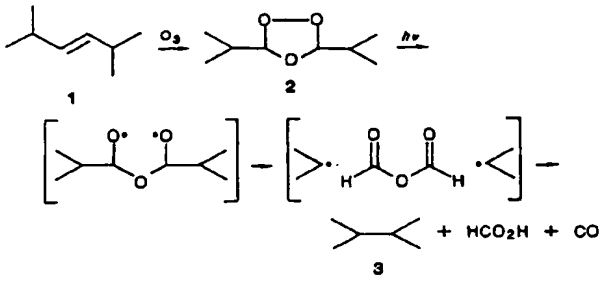
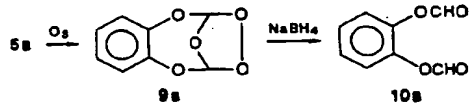


Table I. Photolysis of Ozonides Derived from 1,4-Benzodioxins 5

1,4-benzodioxin	product (% yield)	
	catechol	*o*-benzoquinone
5a	6a (51%)	7a (29%)
5b	6b (47%)	7b (22%)
5c	6c (46%)	7c (17%)
5d	6d (46%)	7d (41%)
5e	6e (92%)	*a*

a Formation of 4-nitro-*o*-benzoquinone (7e) was not detected.

The ozonolysis of 1,4-benzodioxins was carried out at −78 °C in dichloromethane. The attempt to isolate the resulting ozonides failed since the ozonides easily decomposed during the workup procedures. The formation of ozonides was suspected by the fact that 1,2-bis(formyloxy)benzene (10a) was obtained by the treatment of ozonolysis intermediate 9a with sodium borohydride (eq 3).

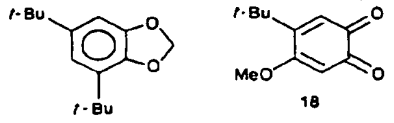


(3)

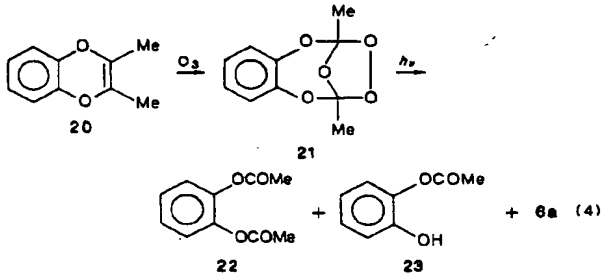
When the resulting solutions of intermediates were irradiated under a high-pressure mercury lamp at −78 °C with a Pyrex filter for 1 h, the corresponding *o*-benzoquinones and catechols were obtained, although 4-nitrocatechol (7e) was obtained exclusively in the case of 6-nitro-1,4-benzodioxin (5e). The yields are summarized in Table I.

Further, only by flash column chromatography after the evaporation of the solvent could *o*-benzoquinones be isolated successfully without polymerization and decomposition. Here, the advantage of the gaseous oxidant was well demonstrated in the isolation of *o*-benzoquinones. Polymerization and decomposition of labile *o*-benzoquinones were reported to be accelerated under aqueous conditions.[9] In this reaction, all procedures can be carried out under nonaqueous conditions. Therefore, in spite of its lability, 4-chloro-*o*-benzoquinone (7c) was obtained in a moderate yield comparable to that of stable 4-*tert*-butyl-*o*-benzoquinone (7b). However, the main products of this reaction were found to be catechols 6. In order to increase the yield of *o*-benzoquinones and to suppress the formation of catechols, the reaction mechanism was investigated.

When 4-*tert*-butyl-*o*-benzoquinone (7b) was treated with carbon monoxide and/or formic acid, *o*-benzoquinone 7b was recovered quantitatively even under heating or irradiation. Further, when *o*-benzoquinone 7b was irradiated in dichloromethane, photoreduction of *o*-benzoquinone 7b did not occur, and *o*-benzoquinone 7b was recovered quantitatively. On the contrary, when *o*-benzoquinone 7b was irradiated in methanol, 4-*tert*-butylcatechol 6b and 4-*tert*-butyl-5-methoxy-*o*-benzoquinone 18 were obtained in 45% and 25% yields, respectively. This fact indicated that catechols might be formed by photoreduction. However, as described later, the methanol adduct such as 18 was not obtained through photolysis of the ozonide derived from 1,4-benzodioxin (5a) in methanol. Therefore, the contribution of the pathways that include a reduction of *o*-benzoquinones, paths a and b, was excluded for the formation of catechols.



Next, the decomposition of ozonide under various conditions was inspected, and the results are summarized in eq 4 and Table II. When 2,3-dimethyl-1,4-benzodioxin



(4)

(20) was treated by the same procedures, catechol 6a and its acetylated compounds, 1,2-diacetoxybenzene (22) and 2-acetoxyphenol (23), were obtained (eq 4). Even by prolonged irradiation, no trace of *o*-benzoquinone 7a could be detected. When ozonolysis intermediate 9b was irradiated at room temperature, the yield of catechol 6b did not increase, and no change was observed in the ratio of the yields of *o*-benzoquinone 7b and catechol 6b (entry a). According to Story's reports, a pathway proceeding through a double β-scission was the major pathway in the photolysis of the ozonides derived from 2,5-dimethyl-3-hexene and cyclopentene.[3] In contrast, pathways including a single β-scission or an intramolecular hydrogen abstraction, such as paths c–e, were the major pathways in the thermal decomposition of the ozonides.[10] If catechols are formed through path c or e, which include an intramolecular hydrogen abstraction, photolysis of the ozonide 21 should no afford catechol 6a, because of the absence of an abstractable hydrogen. Further, if catechols were formed through path c, d, or e, the yield of catechols should increase when suspected ozonide 9 was decomposed at a high temperature (room temperature). Therefore, paths c–e were also ruled out, and it was concluded that diradical 11 decomposes only through a double β-scission to yield *o*-benzoquinones (Scheme II).

In contrast, when ozonolysis intermediate 9a was irradiated in methanol, which is a more protic solvent than dichloromethane, catechol 6a and 2-(formyloxy)phenol (19a) were obtained exclusively, and no trace of *o*-benzoquinone 7a was detected (entry b). Similarly, when 9a was

(9) Forsyth, W. G. C.; Quesnel, V. C. *Biochim. Biophys. Acta* 1957, *25*, 155.

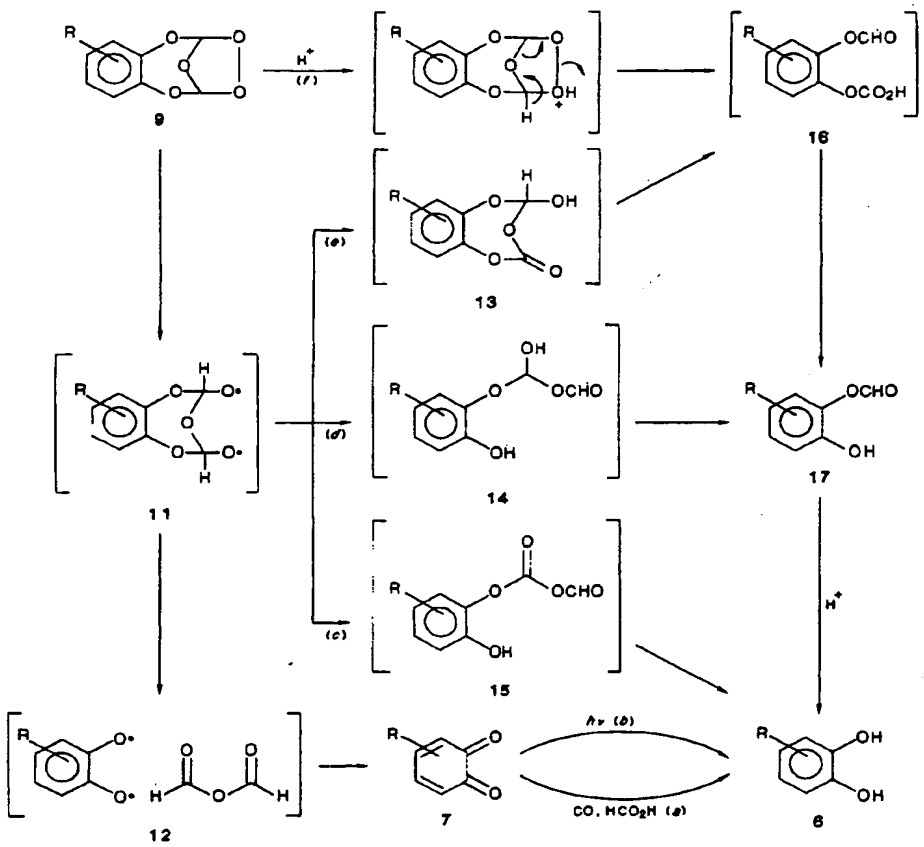
(10) Story, P. R.; Hall, T. K.; Morrison, W. H., III; Farine, J.-C. *Tetrahedron Lett.* 1968, 5397.

Table II. Decomposition of Ozonides Derived from 1,4-Benzodioxins under Various Conditions

entry	1,4-benzodioxin	condition	solvent	product (% yield) catechol	*o*-benzoquinone	2-(formyloxy)phenol
a	**5b**	h/rt/1 h	CH_2Cl_2	**6b** (47%)	**7b** (22%)	*a*
b	**5a**	h/−78 °C/1 h	MeOH	**6a** (53%)	*a*	**17a** (45%)
c	**5a**	dark/CF_3CO_2H/−78 °C/3 h	CH_2Cl_2	**6a** (50%)	*a*	**17a** (19%)
d	**5a**	dark/rt/10 h	MeOH	**6a** (93%)	*a*	*a*
e	**5b**	dark/rt/10 h	MeOH	**6b** (60%)	**7b** (4%)	*a*
f	**5d**	dark/rt/10 h	MeOH	**6d** (75%)	**7d** (17%)	*a*

[a] Formation was not detected.

Scheme II



treated with trifluoroacetic acid without irradiation, a large amount of catechol and 2-(formyloxy)phenol (**19a**) was obtained (entry c). Further, when **9a** was kept in methanol at room temperature without irradiation for 10 h, 2-(formyloxy)phenol (**19a**) was hydrolyzed, and catechol **6a** was obtained in a quantitative yield (entry d). These results indicated that the formation of catechol **6a** was greatly dependent on the polarity and acidity of the solvent. On the other hand, when 1,4-benzodioxins **5b** and **5d** were ozonized in methanol, the formation of catechol **6b** and **6d** was slightly suppressed, and a small amount of *o*-benzoquinone **7b** and **7d** was obtained (entry e and f). Since these 1,4-benzodioxins have a *tert*-butyl group, it was indicated that the formation of catechols would be retarded by the steric hindrance of the bulky substituent group on the benzene nucleus. Therefore, catechols should be formed through the intermolecular ionic decomposition pathway of the ozonides (path f), while *o*-benzoquinones were formed through the intramolecular decomposition pathway that was induced by a homolysis of oxygen–oxygen bond followed by a double β-scission.

Ozonolysis of 2,3-dimethyl-1,4-benzodioxin (**20**) in methanol proceeded in a surprisingly different way, compared to the reaction of 2,3-unsubstituted 1,4-benzodioxins. When 1,4-benzodioxin **20** was treated with ozone in methanol, only an anomalous product, 2,3-dimethyl-3-methoxy-1,4-benzodioxan-2-ol (**26**), was obtained in 64% yield. This anomalous product seemed to be formed directly from a primary ozonide **24**. Owing to the two methyl groups, the primary ozonide **24** seems to be strained at the trioxolane ring and to be reactive toward nucleophiles in order to release the strain. Thus, the primary ozonide **24** would be readily transformed not to the secondary ozonide **21** but to the peroxy derivative **25** by the contact with methanol. By the decomposition of this peroxy derivative **25**, 1,4-benzodioxan-2-ol (**26**) was formed (Scheme III).

Generally, catechols are protected by alkylation or acylation to yield ethers and esters, respectively. However,

Scheme III

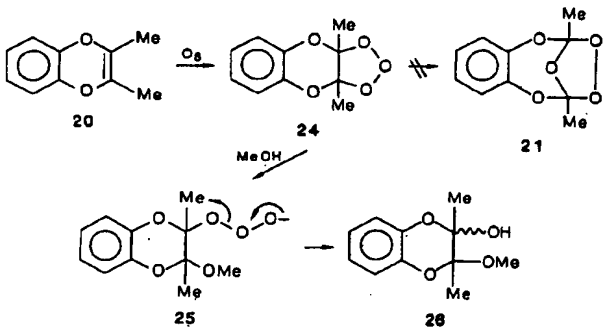


Table III. Ozonolysis of 1,4-Benzodioxins in Methanol

1,4-benzodioxin	product (% yield)	
	catechol	o-benzoquinone
5a	6a (93%e	a
5b	6b (60%)	7b (4%)
5c	6c (88%)	a
5d	6d (75%)	7d (17%)
5e	6e (82%)	a
5f	6f (92%)	a

[a] Formation of o-benzoquinone 7 was not detected.

since the deprotection of ethers and esters is performed by hydrolysis in which severe conditions are required, it is difficult to protect catechols that have substituent groups sensitive to water, acid, base, heat, and so on. Since ozonolysis of 1,4-benzodioxins can be carried out under nonaqueous conditions at low temperature, the application of ozonolysis of 1,4-benzodioxins for the synthesis of catechol derivatives was inspected. When the ozonolysis of 1,4-benzodioxins was carried out at −78 °C in methanol and the resulting intermediates were kept for 10 h at room temperature without irradiation, the corresponding catechols were obtained exclusively except for the case of 1,4-benzodioxins **5b** and **5d**. The yields are summarized in Table III. Therefore, it was additionally indicated that ozonolysis of 1,4-benzodioxins in methanol can be applied to the synthesis of catechol derivatives, especially for the synthesis of commercially unavailable catechols such as 4-benzoylcatechol (**6f**). Also, it was indicated that 1,4-benzodioxins could be applied as a protecting group of catechols.

In conclusion, it was found that photolysis of the ozonides that were derived from 1,4-benzodioxins yielded *o*-benzoquinones and catechols. *o*-Benzoquinones were obtained in moderate yields independent of their stability and of their substituent except the case of the nitro-substituted one, which proceeded by the side reaction on the irradiation. Through the mechanistic studies, it was indicated that *o*-benzoquinones were formed through a radical pathway that includes a homolysis of the oxygen–oxygen bond of the ozonides followed by a double β-scission, while catechols were formed through an ionic pathway that was induced by acidic impurities. Since ozonolysis and photolysis can be performed under a nonaqueous condition at low temperature, and since no complex workup procedure such as extraction would be required, this reaction is expected to be a preferable method for the synthesis and isolation of labile *o*-benzoquinones.

In contrast, when ozonolysis of 1,4-benzodioxins was carried out under protic conditions, catechols were yielded exclusively. This fact indicates additionally that 1,4-benzodioxins can be applied as the starting material as well as the protecting group of catechols.

Experimental Section

Melting points were measured on Yanagimoto micro melting point apparatus and are uncorrected. The IR spectra were measured on a JASCO IRA-1 infrared spectrophotometer. The ^1H and ^{13}C NMR spectra were measured on a JEOL FX-100 (100 MHz) and a FX-90Q (90 MHz) spectrometer, respectively, with tetramethylsilane as an internal standard.

General Procedure for the Preparation of 1,4-Benzodioxins 5a–e.[11] To a solution of 30 mmol of the corresponding catechol and 11.3 g (60 mmol) of 1,2-dibromoethane in 50 mL of ethylene glycol was added 8.7 g (63 mmol) of anhydrous potassium carbonate, and the mixture was heated at 120 °C for 4 h under an argon atmosphere. After heating, the organic material was extracted with dichloromethane, washed with water, and dried over anhydrous magnesium sulfate. After removal of the solvent, the resulting residue was purified by chromatography on silica gel with *n*-hexane/benzene (5/1) as an eluent to give 1,4-benzodioxans.

The mixture of 5 mmol of these 1,4-benzodioxans, 2.1 g (12 mmol) of *N*-bromosuccinimide, and 20 mg of AIBN in 60 mL of carbon tetrachloride was refluxed for 12 h under argon atmosphere. After heating, the yellow precipitate was filtered off, and the organic solution was washed with water and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was dissolved in 50 mL of acetone and refluxed for 2 h with 3.75 g (25 mmol) of sodium iodide under an argon atmosphere. After heating, the organic material was extracted with dichloromethane, washed with aqueous sodium thiosulfate solution, and dried over anhydrous magnesium sulfate. After removal of the solvent, the resulting residue was purified by chromatography on silica gel with *n*-hexane as an eluent to give 1,4-benzodioxins.

1,4-Benzodioxin (5a): bp 48–50 °C/(3 Torr); IR ($CHCl_3$) 1665, 1595, 1490 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.81 (s, 2 H), 6.5–6.8 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 116.3 (d), 124.1 (d), 126.8 (d), and 142.8 (s).

6-*tert*-Butyl-1,4-benzodioxin (5b): bp 55–60 °C/(4 Torr); IR ($CHCl_3$) 1660, 1585, 1495 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (s, 9 H), 5.82 (s, 2 H), 6.51 (d, J = 8.3 Hz, 1 H), 6.63 (d, J = 1.95 Hz, 1 H), 6.80 (dd, J = 1.95, 8.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 31.2 (q), 34.2 (s), 113.6 (d), 115.5 (d), 120.5 (d), 126.7 (d), 126.8 (d), 140.2 (s), 142.0 (s), 147.6 (s). Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.41. Found: C, 75.55; H, 7.37.

6-Chloro-1,4-benzodioxin (5c): IR ($CHCl_3$) 1670, 1595, 1490 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.81 (s, 2 H), 6.48 (d, J = 8.79 Hz, 1 H), 6.58 (d, J = 2.45 Hz, 1 H), 6.74 (dd, J = 2.44, 8.30 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 116.6 (d), 117.0 (d), 123.8 (d), 126.5 (d), 126.8 (d), 128.4 (s), 141.4 (s), 143.1 (s). Anal. Calcd for $C_8H_5ClO_2$: C, 56.99; H, 2.98. Found: C, 56.85; H, 2.94.

5,7-Di-*tert*-butyl-1,4-benzodioxin (5d): mp 38–40 °C (from ethanol); IR (film) 1700, 1670, 1595, 1490 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (s, 9 H), 1.31 (s, 9 H), 5.86 (d, J = 4.9 Hz, 1 H), 5.90, (d, J = 4.9 Hz, 1 H), 6.53 (d, J = 2.4 Hz, 1 H), 6.84 (d, J = 2.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 29.7 (q), 31.3 (q), 34.4 (s), 34.8 (s), 111.7 (d), 118.2 (d), 126.4 (d), 126.9 (d), 136.7 (s), 139.0 (s), 142.5 (s), 145.8 (s). Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.00; H, 9.00. Found: C, 77.81; H, 9.10.

6-Nitro-1,4-benzodioxin (5e): mp 131–132 °C (from ethanol) (lit.[7a] mp 154–155 °C); IR (KBr) 1680, 1595, 1495 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.92 (s, 2 H), 6.69 (d, J = 8.79 Hz, 1 H), 7.48 (d, J = 2.93 Hz, 1 H), 7.75 (dd, J = 2.93, 8.79 Hz, 1 H); ^{13}C ($CDCl_3$) δ 112.0 (d), 113.4 (d), 116.1 (d), 126.6 (d), 127.0 (d), 142.7 (s), 144.0 (s), 148.4 (s). Anal. Calcd for $C_8H_6NO_4$: C, 53.64; H, 2.81; N, 7.81. Found: C, 53.38; H, 2.83; N, 7.72.

6-Benzoyl-1,4-benzodioxin (5f). To the suspension of 300 mg (4 mmol) of aluminum chloride in 20 mL of dichloromethane was added dropwise at 0 °C the solution of 560 mg (4 mmol) of benzoyl chloride in 10 mL of dichloromethane, and the mixture was stirred for 15 min. To this mixture was added dropwise the

(11) Kashima, C.; Tomotake, A.; Omote, Y. *J. Heterocycl. Chem.*, in press.

solution of 540 mg (4 mmol) of 1,4-benzodioxan in 10 mL of dichloromethane, and the resultant mixture was stirred for 1 h at 0 °C. After stirring, the organic materials were washed with diluted hydrochloric acid and water and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo, and the residue was purified on silica gel with *n*-hexane/ethyl acetate (3/1) as an eluent to give 810 mg (85%) of 6-benzoyl-1,4-benzodioxan. 6-Benzoyl-1,4-benzodioxin (**5f**) was prepared from 6-benzoyl-1,4-benzodioxan in the same manner as described before: mp 74–75 °C (from ethanol); IR (KBr) 1670, 1645, 1580, 1490 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.88 (s, 2 H), 6.64 d, J = 8.3 Hz, 1 H), 7.11 (d, J = 1.95 Hz, 1 H), 7.29 (dd, J = 1.95, 8.3 Hz, 1 H), 7.4–7.8 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 115.8 (d), 118.0 (d), 126.5 (d), 127.1 (d), 127.4 (d), 128.2 (d), 129.6 (d), 132.2 (d), 133.7 (s), 137.5 (s), 142.5 (s), 146.7 (s), 194.4 (s). Anal. Calcd for $C_{15}H_{10}O_3$: C, 75.62; H, 4.23. Found: C, 75.34; H, 4.25.

4,6-Di-*tert*-butyl-1,3-benzodioxolane (8). To the solution of 6.7 g (30 mmol) of 3,5-di-*tert*-butylcatechol in 300 mL of dichloromethane were added 6.8 g (30 mmol) of triethylbenzylammonium chloride and 100 mL of an aqueous solution of sodium hydroxide (30%). After the mixture was stirred for 1 day at room temperature, the aqueous layer was separated, and the organic layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo, and the residue was purified on silica gel with *n*-hexane/benzene (5/1) as an eluent to give 3.2 g (42%) of 1,4-benzodioxan along with 3.2 g (54%) of the titled compound: IR (film) 1600, 1490 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (s, 9 H), 1.35 (s, 9 H), 5.85 (s, 2 H), 6.78 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 29.7 (q), 31.8 (q), 34.1 (s), 34.8 (s), 100.0 (t), 104.3 (d), 115.4 (d), 131.8 (s), 142.6 (s), 144.6 (s), 147.4 (s); MS, m/e 234, 219. Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.98; H, 9.52.

1,2-Bis(formyloxy)benzene (10a). To the solution of 140 mg (1 mmol) of 1,4-benzodioxin (**5a**) in 10 mL of dichloromethane was bubbled ozone containing an oxygen stream at −78 °C until the solution turned blue. The excess ozone was removed with bubbling argon, and 190 mg (5 mmol) of sodium borohydride was added. After being stirred at room temperature for 5 h, the reaction mixture was washed with water and dried over anhydrous magnesium sulfate, and the solvent was removed in vacuo. The residue was purified on silica gel with dichloromethane/acetone (30/1) as an eluent to give 30 mg (18%) of the titled compound: ^1H NMR[12b] ($CDCl_3$) δ 7.2–7.4 (m, 4 H), 8.25 (s, 2 H).

General Procedure for Photolysis of the Ozonides Derived from 1,4-Benzodioxins. To the solution of 2 mmol of 1,4-benzodioxins in distilled 20 mL of dichloromethane was bubbled ozone containing an oxygen stream at −78 °C until the solution turned blue. The excess ozone was removed with bubbling argon, and the solution was irradiated by a high-pressure mercury lamp (100 W) with a Pyrex filter for 1 h at −78 °C. After irradiation, the solvent was removed in vacuo, and the residue was purified on silica gel with dichloromethane/acetone (30/1) as an eluent. Catechols **6a–e** were identified with authentic samples.

***o*-Benzoquinone (7a):** IR ($CHCl_3$) 1690, 1665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.2–6.4 (m, 2 H), 6.9–7.1 (m, 2 H).

4-*tert*-Butyl-*o*-benzoquinone (7b): mp 67–68 °C (from *n*-hexane/ether) (lit.[13] mp 68 °C); IR (KBr) 1645, 1625, 1605 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.3 (s, 9 H), 6.3 (d, J = 2.4 Hz, 1 H), 6.4 (d, J = 9.8 Hz, 1 H), 7.3 (dd, J = 2.4, 9.8 Hz, 1 H).

4-Chloro-*o*-benzoquinone (7c): IR ($CHCl_3$) 1695, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.4 (d, J = 9.3 Hz, 1 H), 6.6 (d, J = 2.3 Hz, 1 H), 7.0 (dd, J = 2.3, 9.3 Hz, 1 H).

3,5-Di-*tert*-butyl-*o*-benzoquinone (7d): mp 114–115 °C (from *n*-hexane) (lit.[14] mp 114–115 °C); IR (KBr) 1630, 1605, 1550 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (s, 9 H), 1.28 (s, 9 H), 6.21 (d, J = 2.44 Hz, 1 H), 6.96 (d, J = 2.44 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 27.6 (q), 29.2 (q), 35.4 (s), 36.0 (s)8 122.0 (d), 133.4 (d), 149.9 (s), 163.2 (s), 180.0 (s), 181.0 (s).

Attempt To Reduce 4-*tert*-Butyl-*o*-benzoquinone (7b) with Carbon Monoxide and Formic Acid. To the solution of 330 mg (2 mmol) of 4-*tert*-butyl-*o*-benzoquinone (**7b**) in 20 mL of distilled dichloromethane and 2 mL of formic acid was bubbled carbon monoxide for 15 min at room temperature. Then the solution was heated under reflux or irradiated for 1 h. After that, *o*-benzoquinone **7b** was recovered completely.

Photoreduction of 4-*tert*-Butyl-*o*-benzoquinone (7b) in Methanol. The solution of 160 mg (1 mmol) of 4-*tert*-butyl-*o*-benzoquinone (**7b**) in 15 mL of distilled methanol was irradiated by a high-pressure mercury lamp (100 W) with a Pyrex filter at room temperature for 1 h. After irradiation, the solvent was removed in vacuo, and the residue was purified on silica gel with dichloromethane/acetone (50/1) as an eluent to give 42 mg (45%) of 4-*tert*-butylcatechol and 25 mg (27%) of the starting material **7b** along with 30 mg (25%) of 4-*tert*-butyl-5-methoxy-*o*-benzoquinone (**18**): IR ($CHCl_3$) 1645, 1605, 1550 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 (s, 9 H), 3.92 (s, 3 H), 5.79 (s, 1 H), 6.28 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.7 (q), 36.4 (s), 103.5 (d), 125.8 (d), 159.0 (s), 170.7 (s), 178.8 (s), 181.6 (s).

Ionic Decomposition of the Ozonide. The solution of 130 mg (1 mmol) of 1,4-benzodioxin **5a** in 20 mL of distilled dichloromethane was ozonized at −78 °C, and then the solution of 100 mg of trifluoroacetic acid in 5 mL of dichloromethane was added to this solution. After the mixture stood for 3 h at −78 °C, the solvent was removed in vacuo, and the residue was purified on silica gel with chloroform/acetone/ethanol (100/5/1) as an eluent to give 55 mg (50%) of catechol **6a** along with 30 mg (19%) of 2-(formyloxy)phenol (**17a**); ^1H NMR ($CDCl_3$) δ 7.0–7.2 (m, 4 H), 8.8 (s, 1 H).

2,3-Dimethyl-1,4-benzodioxin (20). The solution of 2.2 g (20 mmol) of catechol **5a** in 40 mL of freshly distilled ethanol was added onto 1 g (44 mmol) of sodium under argon atmosphere at 0 °C. After evaporation of hydrogen ceased, the solution of 2.2 g (22 mmol) of 3-chloro-2-butanone in 20 mL of freshly distilled ethanol was added dropwise to the resulting clear-blue solution, and the mixture was heated for 5 h under reflux. After the mixture was stirred the solvent was removed in vacuo to its half volume, and the organic materials were extracted with dichloromethane. The organic layer was washed with water and dried over magnesium sulfate, and the solvent was removed in vacuo. The residue was purified on silica gel with chloroform/acetone/ethanol (100/5/1) to give 2.5 g (69%) of 2,3-dimethyl-1,4-benzodioxan-2-ol: mp 83–84 °C (from dichloromethane/hexane); IR (KBr) 3380, 1600, 1495 cm^{-1}; ^1H NMR ($CDCl_2$) δ 1.28 (d, J = 6.35 Hz, 0.9 H), 1.38 (d, J = 6.35 Hz, 2.1 H), 1.46 (s, 0.9 H), 1.51 (s, 2.1 H), 3.40 (br s, D_2O exchangeable, 0.7 H), 3.57 (br s, D_2O exchangeable, 0.3 H), 3.89 (q, J = 6.35 Hz, 0.3 H), 4.04 (q, J = 6.34 Hz, 0.7 H), 6.85 (s, 4 H); ^{13}C NMR ($CDCl_3$) δ 15.2 (q), 15.4 (q), 21.6 (q), 23.1 (q), 74.5 (d), 74.9 (d), 95.4 (s), 95.8 (s), 116.8 (d), 117.3 (d), 117.5 (d), 121.4 (d), 121.7 (d), 121.9 (d), 122.3 (d), 140.6 (s), 141.3 (s), 142.7 (s). Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.54; H, 6.76. To the solution of 720 mg (4 mmol) of this compound in 10 mL of distilled pyridine was added dropwise at 0 °C 600 mg (5 mmol) of thionyl chloride. After the mixture was stirred for 5 h at room temperature, pyridine was removed by shaking with diluted hydrochloric acid, and the organic materials were extracted with dichloromethane and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was dissolved in a mixture of 20 mg of *p*-toluenesulfonic acid in 10 mL of benzene, and the mixture was heated for 1 h under reflux. The solvent was removed in vacuo, and the residue was purified on silica gel with *n*-hexane/benzene (6/1) as an eluent to give 1.3 g (63%) of the titled compound: mp 37.5–38.5 °C (from *n*-hexane) (lit.[12a] mp 38–39 °C); IR ($CHCl_3$) 1730, 1600, 1490 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.73 (s, 6 H), 6.6–6.8 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 14.4 (q), 115.4 (d), 123.2 (d), 128.1 (s), 143.0 (s).

1,2-Diacetoxybenzene (**22**) (69 mg (35%)), 2-acetoxyphenol (**23**) (23 mg (15%)), and catechol **6a** (39 mg (39%)) were obtained in the ozonolysis–photolysis of 1,4-benzodioxin **20** in the same manner as described before.

1,2-Diacetoxybenzene (22): IR (film) 1760, 1590, 1490 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.2 (s, 6 H), 7.1 (s, 4 H).

2-Acetoxyphenol (23): IR ($CHCl_3$) 3560, 1760, 1605, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.1 (s, 3 H), 7.2 (br s, 4 H).

General Procedure for Ozonolysis of 1,4-Benzodioxins in Methanol. The solution of 1 mmol of 1,4-benzodioxins **5** and

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(13) Teuber, H.-J.; Staiger, G. *Chem. Ber.* **1955**, *88*, 802.

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20 in 15 mL of distilled methanol was ozonized at −78 °C. After removal of the excess ozone, the solution was stood for 10 h at room temperature. The solvent was removed in vacuo, and the residue was purified on silica gel with chloroform/acetone/ethanol (100/10/2) as an eluent.

4-Benzoylcatechol (6f): mp 205–207 °C (from ethanol); IR (KBr) 3300, 1730, 1620, 1590, 1580, 1560, 1520 cm^{-1}; ^1H NMR (CD_3OD) δ 4.9 (br s, D_2O exchangeable, 2 H), 6.87 (d, J = 8.3 Hz, 1 H), 7.2–7.8 (m, 7 H); ^{13}C NMR (CD_3OD) δ 15.5 (d), 117.9 (d), 125.4 (d), 128.9 (d), 130.0 (s), 130.3 (d), 132.6 (d), 139.4 (s), 146.0 (s), 151.7 (s), 197.6 (s). Anal. Calcd for $C_{13}H_{10}O_3$: C, 72.88; H, 4.70. Found: C, 72.81; H, 4.71.

Cis–Trans Mixture of 2,3-Dimethyl-3-methoxy-1,4-benzodioxan-2-ol (26): mp 125–127 °C (from *n*-hexane); IR (KBr) 3400, 1580, 1470 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.60 (s, 6 H), 3.20 (s, 1 H), 3.24 (s, 2 H), 6.88 (s, 4 H); ^{13}C NMR ($CDCl_3$) δ 17.3 (q), 22.1 (q), 49.3 (q), 96.1 (s), 98.6 (s), 117.2 (d), 117.5 (d), 121.7 (d), 122.5 (d), 139.8 (s), 141.1 (s); MS, m/e 210. Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found: C, 62.93; H, 6.72.

Registry No. **5a**, 255-37-8; **5a** (2,3-dihydro deriv), 493-09-4; **5b**, 110306-99-5; **5b** (2,3-dihydro deriv), 93591-46-9; **5c**, 67470-96-6; **5c** (2,3-dihydro deriv), 57744-68-0; **5d**, 110307-00-1; **5d** (2,3-dihydro deriv), 110851-10-0; **5e**, 67470-95-5; **5e** (2,3-dihydro deriv), 16498-20-7; **5f**, 110851-11-1; **5f** (2,3-dihydro deriv), 93637-87-7; **6a**, 120-80-9; **6b**, 98-29-3; **6c**, 2138-22-9; **6d**, 1020-31-1; **6e**, 3316-09-4; **6f**, 10425-11-3; **7a**, 583-63-1; **7b**, 1129-21-1; **7c**, 31222-02-3; **7d**, 3383-21-9; **8**, 29619-33-8; **9a**, 110851-16-6; **9b**, 110851-17-7; **9c**, 110851-18-8; **9d**, 110851-19-9; **9e**, 110851-20-2; **9f**, 110851-21-3; **10a**, 91201-66-0; **17a**, 110851-12-2; **18**, 36122-03-9; **20**, 79792-92-0; **21**, 110851-22-4; **22**, 635-67-6; **23**, 2848-25-1; **24**, 110851-23-5; *cis*-**26**, 110851-23-5; *trans*-**26**, 110851-15-5; $Br(CH_2)_2Br$, 106-93-4; H_3C-$COCHClCH_3$, 4091-39-8; 2,3-dimethyl-1,4-benzodioxan-2-ol, 110851-13-3.

Notes

P_2O_5/DMSO/Triethylamine (PDT): A Convenient Procedure for Oxidation of Alcohols to Ketones and Aldehydes

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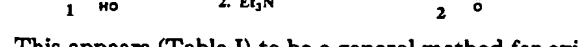
Received July 9, 1987

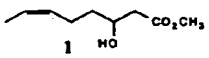
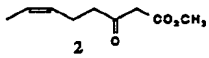
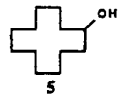
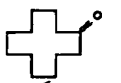
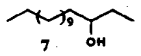
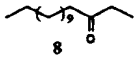
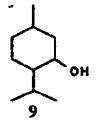
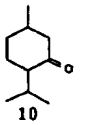
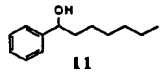
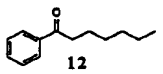
We recently faced the problem of oxidizing alcohol **1** (Table I) to the corresponding ketone **2** on a large scale. Swern oxidation of **1**[1] gave chlorinated products, indicating that oxidation procedures involving positive halogen[2] would be unacceptable. Chromic acid oxidation gave **2** only in low yield, accompanied by polar byproducts. While PCC oxidation[3] proceeded in reasonable yield, separation of the product from the chromium-containing residue was cumbersome.

Pursuing Moffatt oxidation,[4] we found references in the carbohydrate literature to the use of P_2O_5[5] to activate DMSO. Ketone formation, however, required long reaction times. By analogy to the Swern procedure, it seemed reasonable that triethylamine[6,7] might accelerate transformation of the initial (uncharacterized) adduct to the ketone. In fact, addition of P_2O_5 (1.8 equiv) to a solution of alcohol **1** (1.0 equiv) and DMSO (2.0 equiv) in CH_2Cl_2 at room temprature leads to immediate disappearance of starting material, with formation of a suspension. On addition of triethylamine (3.5 equiv), the suspension dissolves, and ketone **2** is liberated.



This appears (Table I) to be a general method for oxidation of alcohols to ketones and aldehydes. It is advan-

Table I. Oxidation of Alcohols by PDT[a]

starting alcohol	product	yield[b] %
 1	 2	85
$CH_3(CH_2)_{15}OH$ 3	$CH_3(CH_2)_{14}CH{=}O$ 4	83
 5	 6	86
 7	 8	81
 9	 10	82
 11	 12	83
 13[c]	 14[c]	90[d]

Ar = 1-naphthyl

[a] Phosphorus pentoxide/dimethyl sulfoxide; triethylamine. [b] Yields are for pure, isolated material. [c] Reference 8. [d] In this case, the reaction proceeded to only about 50% conversion.

(1) Muncusco, A. J.; Huang, S. L.; Swern, D. J. *J. Org. Chem.* **1978**, *43*, 2480.
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(3) Covey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, *16*, 2647.
(4) (a) Pfitzner, K. E.; Moffatt, J. G. *J. Am. Chem. Soc.* **1963**, *85*, 3027. (b) Moffatt, J. G. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 242.
(5) (a) Onodera, K.; Hirano, S.; Kashimura, N. *J. Am. Chem. Soc.* **1965**, *87*, 4651. (b) Georges, M.; Fraser-Reid, B. *J. Org. Chem.* **1985**, *50*, 5754.
(6) Triethylamine has been used in conjunction with P_2O_5 and DMSO, but not to effect alcohol oxidation: Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.
(7) Alternative bases (K_2CO_3, pyridine) gave reversion to the starting alcohol, with little if any oxidation.

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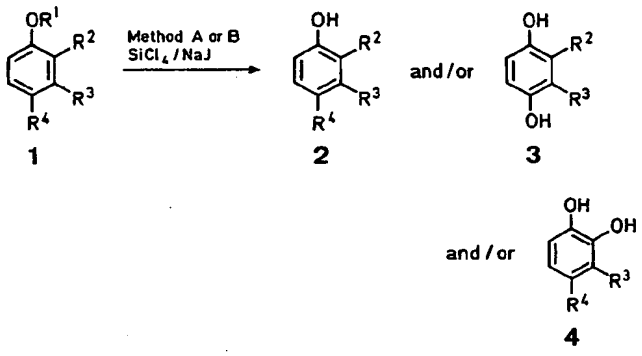
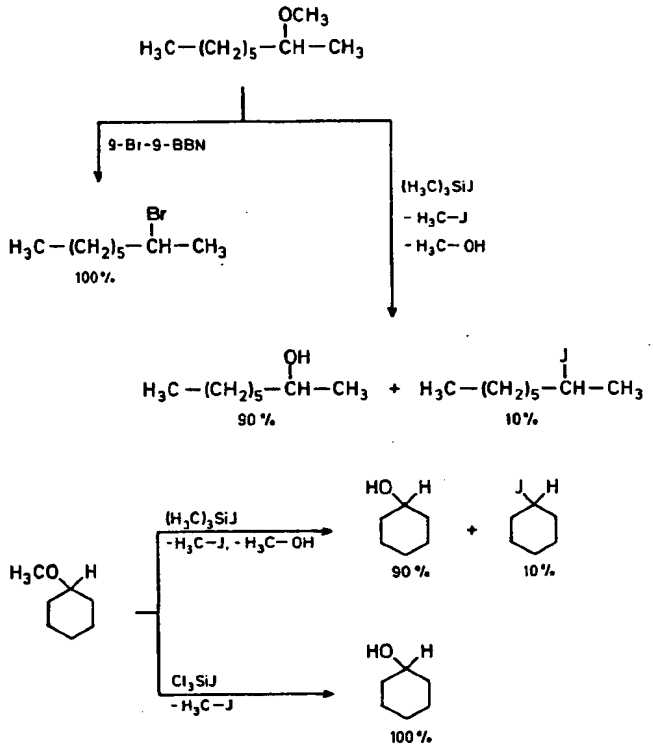
ion practically stops at the first stage and yields iodotrichlorosilane under these conditions. A variety of aryl alkyl and alkyl alkyl ethers are cleaved in good yields to give alkyl iodides and silyl ethers. The initially formed aryl or alkyl silyl ethers are hydrolysed to phenols or alcohols, respectively, during the aqueous work-up and are isolated as such (Table 1).



The cleavage patterns of iodotrichlorosilane and iodotrimethylsilane[1,2,3,4] are similar to each other but complementary to that of boron reagents such as 9-bromo-9-borabicyclo[3.3.1]nonane[5]. A comparison of the cleavage pattern of cyclohexyl methyl ether shows that iodotrichlorosilane is more regiospecific than iodotrimethylsilane.



Silicon Tetrachloride/Sodium Iodide as a Convenient and Highly Regioselective Ether Cleaving Reagent

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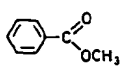
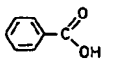
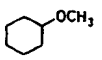
We report here that the system silicon tetrachloride/sodium iodide in dichloromethane/acetonitrile is a highly regioselective and versatile reagent for the cleavage of ethers. Halogen analysis of the distillate indicates that the exchange of iodide

The yields of the cleavage products of anisole and 1,3-benzodioxole with iodotrichlorosilane and iodotrimethylsilane indicate that they are of comparative reactivity with iodotrichlorosilane being somewhat more reactive (Table 2). It was found that the use of iodotrichlorosilane is compatible with com-

0039-7881/82/1232-1048 $ 03.00

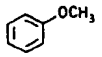
Table 1. Cleavage of Ethers 1 with Silicon Tetrachloride/Sodium Iodide

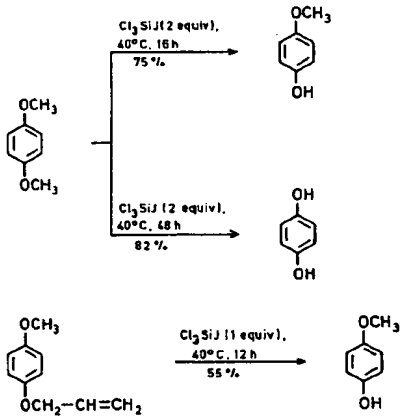
Substrate R^1	R^2	R^3	R^4	Product[a] type	Yield[b] [%]	Method	Mol.-equiv. of reagent	Reaction time	m.p. [°C] or b.p. [°C]/torr found	reported
CH_3	H	H	H	2	20	A	1	16 h	182°/760	182°/760[b]
CH_3	H	H	H	2	78	B	1	16 h		
C_2H_5	H	H	H	2	59	B	1	20 h		
i-C_3H_7	H	H	H	2	80	A	1	14 h		
$C_6H_5CH_2$	H	H	H	2	82	A	1	6 h		
$H_2C{=}CH{-}CH_2$	H	H	H	2	84	A	1	8 h		
$H_2C{=}CH{-}CH_2$	H	H	H_3CO	2	55	A	1	12 h	243°/760	243°/760[7]
$H_2C{=}CH{-}CH_2$	H	H	H_3CO	2 3	65 14	A	2	12 h	243°/760 170°/760	243°/760[7] 170°/760[8]
H_3C	H	H	H_3CO	2	75	A	2	16 h		
H_3C	H	H	H_3CO	3	82	B	2	48 h		
H_3C	H_3CO	H	H	4	83	B	2	12 h	104°	105°[9]
H_3C	HO	H	H	4	90	B	1	12 h	105°	105°[9]
H_3C	$-(CH{=}CH)_2-$		H	2	66	B	2	24 h	94°	94°[10]
H_3C	H	$-(CH{=}CH)_2-$		2	69	B	2	24 h	121°	123°[10]
$-O-CH_2-O-$		H	H	4	59	B	2	48 h	105°	105°[9]
H_3C	H	H	$H_2C{=}CH{-}CH_2$[17]	4	67	B	2	20 h	120°/12	120°/12[11]
H	H_3CO	H	$H_2C{=}CH{-}CH_2$[18]	4	62	B	2	20 h	139°/4	139°/4[12]
H_3C	H	H	$H_3C{-}CH{=}CH{-}$[19]	2 polymer	11 52	B	1	20 h	138°/14 —	138–140°/14[13] —

Substrate	Product[a]						
		42	B	1	16 h	120°	122°[14]
	J–$(CH_2)_4$–OH	73	A	1	6 h	105°[c]	104.5°[c,15]
		~100	A	1	4 h	160°/760	161°/760[16]

[a] All products displayed appropriate I.R. and ^{1}H-N.M.R. spectra and gave a single spot on T.L.C. analysis.
[b] Yield of isolated product.
[c] m.p. of *p*-nitrobenzoate derivative.

Table 2. Comparison of the Reactivities of Iodotrimethylsilane and Iodotrichlorosilane in Acetonitrile/Toluene at 80 °C

Substrate	Product	Mol-equiv. of reagent	Reaction time	Yield [%] with $JSi(CH_3)_3$	Yield [%] with $JSiCl_3$
		1	16 h	64	78
		2	48 h	18	59



pounds containing double bonds but not with those containing ester groups. We are studying the reactivity of iodotrichlorosilane in different solvent systems to determine whether it is possible to selectively cleave ethers without affecting ester groups.

The rates of cleavage of various alkyl phenyl ethers are sufficiently different to enable the selective cleavage of only one among the various ether groups. For example, *p*-dimethoxybenzene is cleaved to give *p*-methoxyphenol in 75% yield. Also, allyl ether groups are cleaved in preference to methyl ether groups.

Preliminary experiments with acetals indicate that these compounds are cleaved by iodotrichlorosilane quantitatively to the respective aldehyde or ketone at room temperature.

Cleavage of Ethers with Silicon Tetrachloride/Sodium Iodide; Typical Procedures:

Method A: Allyl phenyl ether (2.68 g, 20 mmol) and sodium iodide (3.3 g, 22 mmol) are dissolved in 1:1 dichloromethane/acetonitrile (20 ml). Silicon tetrachloride (2.5 ml, 22 mmol) is added from a dry sy-

ringe and the mixture is stirred and heated under reflux for 8 h. The mixture is then hydrolysed by pouring into water (50 ml) and extracted with ether (2 × 50 ml). The phenol is extracted from the ether layer with 10% sodium hydroxide solution (20 ml), the extract is acidified, and extracted with ether. The ether is evaporated and the phenol obtained by distillation of the residue; yield: 1.56 g (84%); one spot on T.L.C. (silica gel, 1 : 3 ethyl acetate/hexane).

Method B: *o*-Dimethoxybenzene (2.76 g, 20 mmol) and sodium iodide (6.6 g, 44 mmol) are added to 1 : 1 acetonitrile/toluene (30 ml). Silicon tetrachloride (5 ml, 44 mmol) is added and the mixture is stirred and heated under reflux for 12 h. Catechol is isolated from the reaction mixture as described in Method A.

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A Novel $B(C_6F_5)_3$-Catalyzed Reduction of Alcohols and Cleavage of Aryl and Alkyl Ethers with Hydrosilanes†

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The primary alcohols **1a–e** and ethers **4a–d** were effectively reduced to the corresponding hydrocarbons **2** by $HSiEt_3$ in the presence of *catalytic amounts* of $B(C_6F_5)_3$. To the best of our knowledge, this is the first example of catalytic use of Lewis acid in the reduction of alcohols and ethers with hydrosilanes. The secondary alkyl ethers **4j,k** enabled cleavage and/or reduction under similar reaction conditions to produce either the silyl ethers **3m–n** or the corresponding alcohol **5a** upon subsequent deprotection with TBAF. It was found that the secondary alcohols **1g–i** and tertiary alcohol **1j**, as well as the tertiary alkyl ether **4l**, did not react with $HSiEt_3/(B(C_6F_5)_3$ reducing reagent at all. The following relative reactivity order of substrates was found: primary ≫ secondary > tertiary. A plausible mechanism for this nontraditional *Lewis acid catalyzed* reaction is proposed.

Reactions of hydrosilanes in the presence of Lewis acids are very important tools in modern synthetic organic chemistry. Thus, the Lewis acid-catalyzed hydrosilylation of carbon–carbon unsaturated systems is a powerful approach for the synthesis of various types of organylsilanes,[1] whereas the Lewis acid-catalyzed reduction of carbonyl function equivalents with hydrosilanes serves as a useful synthetic tool for the preparation of alcohols.[2] Another area of application of Lewis acid–hydrosilane combination is the reduction of alcohols and ethers. The known reducing methods of this type require *at least stoichiometric amounts of Lewis acid*.[3] Furthermore, the previous methods are most effective for the reduction of C–O bond at tertiary carbon,[3] much less effective for the reduction of secondary substrates,[4] and absolutely noneffective for that of primary alcohols[5] and ethers (Scheme 1).[3] Such reactivity order of tertiary, secondary, and primary substrates is well understood in terms of the classical S_N1 mechanistic pathway (Scheme 1).[3]

We have recently communicated[6] the following: (1) even catalytic amount of $B(C_6F_5)_3$ is enough to effectively reduce certain alcohols and ethers with $HSiEt_3$; (2) the reactivity order for the reduction of tertiary, secondary, and primary substrates with $HSiEt_3$/cat.-$B(C_6F_5)_3$ is completely reverse from that of the traditional $HSiR_3$/Lewis acid reducing systems (Scheme 2).[3] In this paper, we report a full account on this $B(C_6F_5)_3$-catalyzed reaction, involving reduction of alcohols and reductive cleavage of alkyl and aryl ethers, as well as mechanistic studies of these novel transformations.

Results and Discussion

$B(C_6F_5)_3$-Catalyzed Reduction of Alcohols with Hydrosilanes. During our studies on the $B(C_6F_5)_3$-catalyzed hydrostannation of carbon–carbon multiple bonds,[7] we noticed remarkably strong affinity of $B(C_6F_5)_3$ toward the hydride of hydrostannanes.[8] This fact, together with the exceptionally high stability of $B(C_6F_5)_3$,[8] encouraged us to investigate the possibility of reduction of C–O bonds with hydrosilanes in the presence of *catalytic* amounts of this unique Lewis acid (eq 1). In a test experiment, we found that 1-hexadecanol (**1a**) underwent complete dehydrocondensation with 1.1 equiv of $HSiEt_3$ in the presence of 5 mol % of $B(C_6F_5)_3$ to give the corresponding silyl ether **3a** (Table 1, entry 1).[9] Surpris-

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(5) Recently an effecient one-pot radical-initiated reduction of primary and secondary alcohols with Et_3SiH was reported, see: Ferreri, C.; Costantino, C.; Chatgilialoglu, C.; Boukherroub, R.; Manuel, G. *J. Organomet. Chem.* **1998**, *554*, 135.

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(8) Strong affinity of $B(C_6F_5)_3$ toward hydride of hydrosilanes is well-known; for a review, see: Piers, W. E.; Chivers, T. *Chem. Soc. Rev.* **1997**, *26*, 345. See also ref 2d.

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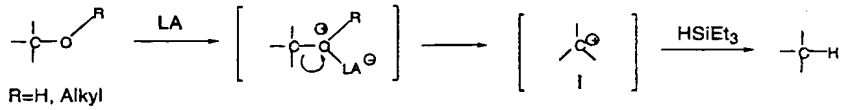
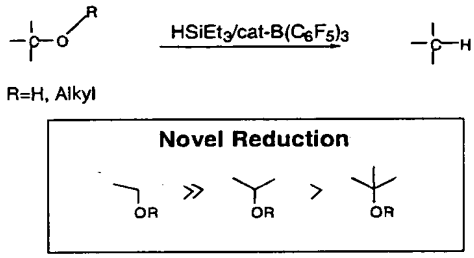
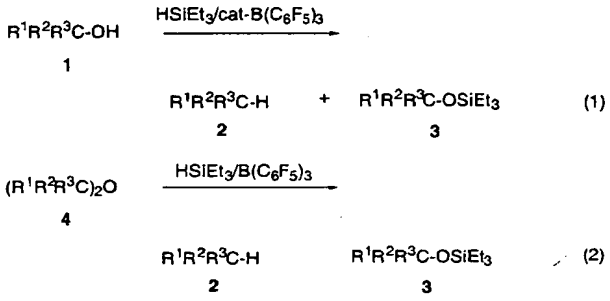
Scheme 1. Traditional Reduction of Alcohols and Ethers with Stoichiometric LA–$HSiEt_3$ System



Scheme 2. Novel Reduction of Alcohols and Ethers with Catalytic $B(C_6F_5)_3$–$HSiEt_3$ System





ingly, we found that in the presence of 3 equiv of $HSiEt_3$ the primary alcohol **1a** was quantitatively reduced into *n*-hexadecane (**2a**, entry 2).[10] All other primary alcohols tested (**1b–e**) under the same reaction conditions (see the Experimental Section for details) were also smoothly reduced into the corresponding hydrocarbons **2b–e** in high to quantitative yields (entries 3–6). Other hydrosilanes tested, such as $HSiPh_3$, $HSiMePh_2$, and $HSiMeEt_2$, were similarly effective. As expected, phenol (**1f**) did not undergo reduction even in the presence of 6 equiv of hydrosilane, the phenyl triethylsilyl ether **3b** was obtained quantitatively, instead (entry 7). Surprisingly again, the secondary alcohols **1g–i**, in contrast to primary ones, produced the silyl ethers **3c–e** in essentially quantitative yields (entries 8–10), thus exhibiting a complete resistance toward the reduction.[11] The tertiary alkyl alcohol (**1j**) did not undergo the reduction at all but gave 96% of the dehydrocondensation product, silyl ether, **3f** (entry 11). In contrast to the alkyl analogues, the secondary alcohol **1k**, possessing two phenyl groups and tertiary trityl alcohol (**1l**), smoothly underwent the reduction even upon treatment with 1.1 equivalents of hydrosilane to give diphenylmethane **2f** and triphenylmethane (**2g**) almost quantitatively (entries 12 and 13, Table 1).

$B(C_6F_5)_3$-Catalyzed Cleavage and/or Reduction of Alkyl Ethers with Hydrosilanes. Inspired by the successful reduction of alcohols with $HSiEt_3$/cat-$B(C_6F_5)_3$ (eq 1, Table 1), we attempted to apply this new reducing system for the reduction of ethers **4** (eq 2, Table 2). It was found that stoichiometric amounts of $HSiEt_3$, in the presence of 5 mol % $B(C_6F_5)_3$, enabled the cleavage of linear primary alkyl ethers **4a,b** into the corresponding hydrocarbons **2a,e** and silyl ethers **3a,h**, respectively (Table 2, entries 1 and 3), whereas in the presence of excess amounts of $HSiEt_3$, **4a,b** underwent smooth exhaustive reduction into the hydrocarbons **2a,e** in quantitative to high yields, respectively (entries 2 and 4). Very similarly, reduction of a cyclic primary ether **4c** in the presence of 1.1 equiv of $HSiEt_3$/10 mol % $B(C_6F_5)_3$ gave the corresponding ring-cleaved silyl ether **3i** in 96% yield (entry 5). Here again, the use of 3.0 equiv of $HSiEt_3$/10 mol % $B(C_6F_5)_3$ afforded the corresponding hydrocarbon **2h** (entry 6). Phthalan (**4d**) was easily reduced into the *o*-xylene in 78% yield (**2i**, entry 7). As expected, the aryl C–O bonds in 2,3-dihydrobenzofuran (**4e**) and methylenedioxybenzene (**4i**) were tolerant toward the reduction, and consequently, the cleavage products triethylsilyl ether of *o*-ethylphenol (**3j**) and catechol (**5a**) were produced in quantitative and 79% yields, respectively (entries 8, 12). Similarly, anisole derivatives **4f,g,h** were readily cleaved to form the corresponding phenyl silyl ethers **3b,k,l** in virtually quantitative isolated yields (entries 9–11). This method could serve as a useful tool for the deprotection of alkyl aryl ethers, because it allows one to perform a quantitative demethylation of anisoles under very mild conditions,[12] unlike the known methods.[13] Obviously, TES-ethers of phenols can be easily desilylated in situ by a variety of known procedures.[13] It was interesting to find that the secondary alkyl ether **4j** in the presence of 3 equiv of $HSiEt_3$ was quantitatively cleaved to give the silyl ether **3m** (entry 13). Thus, the secondary alkyl silyl ether **3m** (as well as the secondary

(9) While our project was underway, a paper describing silylation of alcohols in the presence of $HSiEt_3/B(C_6F_5)_3$ system was published; see: Blackwell, J. M.; Foster, K. L.; Beck, V. H.; Piers, W. E. *J. Org. Chem.* **1999**, *64*, 4887.

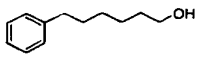
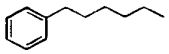
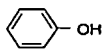
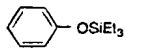
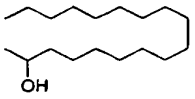
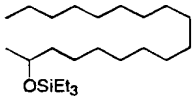
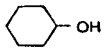
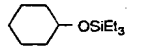
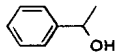
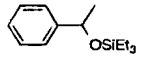
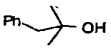
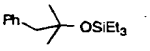
(10) It is well-known that primary alcohols and ethers do not undergo reduction with traditional hydrosilane/Lewis acid reducing system; see refs 3 and 4.

(11) The observed reduction of primary alcohols and resistance of secondary alcohols toward reduction by $HSiEt_3/B(C_6F_5)_3$ system is absolutely opposite to the reactivity order which was observed in the reduction of alcohols by the classical methods; see refs 3 and 4 (eq 1).

(12) Although reproducible results were obtained with 5 mol % of commercially available boron catalyst, it was found that the freshly prepared catalyst was notably more efficient. Thus, only 1 mol % of $B(C_6F_5)_3$ was enough for the complete cleavage of anisoles **4g,h**. For the routine synthesis of $B(C6F_5)_3$, see: Massey, A. G.; Park, A. J. *J. Organomet. Chem.* **1964**, *2*, 245.

(13) Greene, T. W.; Wuts, P. G. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999.

Table 1. Reduction of Alcohols 1 with $HSiR_3$/Cat.-$B(C_6F_5)_3$ System

Entry	Alcohol 1	$HSiEt_3$ (eq)	Products (Isolated Yield, %)
1	n-$C_{16}H_{33}OH$ (a)	1.1	n-$C_{16}H_{33}OSiEt_3$ (3a) (>99)
2	//	3.0	n-$C_{16}H_{34}$ (2a) (95)
3	 (b)	6.0	 (2b) (>99)
4	$Ph(CH_2)_3OH$ (c)	3.0	$Ph(CH_2)_3H$ (2c) (>95)[a]
5	$Ph(CH_2)_2OH$ (d)	//	$Ph(CH_2)_2H$ (2d) (>95)[a]
6	$PhCH_2OH$ (e)	6.0	$PhCH_3$ (2e) (78)[a]
7	 (f)	//	 (3b) (>99)[b]
8	 (g)	3.0	 (3c) (>99)
9	 (h)	6.0	 (3d) (>95)[a]
10	 (i)	//	 (3e) (>95)[a]
11	 (j)	//	 (3f) (96)
12	Ph_2CHOH (k)	1.1	Ph_2CH_2 (2f) (98)
13	Ph_3COH (l)	1.1	Ph_3CH (2g) (98)

[a] NMR yield. [b] GC yield.

alkyl alcohols, see also Table 1, entries 8–10) exhibited striking resistance toward reduction. Cyclic secondary ether **4k** behaved similarly, producing the cleavage product **3n** in very high yield (entry 14). Ether **4l**, possessing both tertiary and primary alkyl units, did not undergo reduction at all (entry 13).[14]

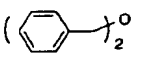
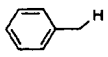
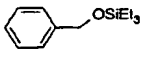
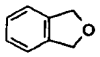
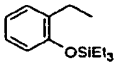
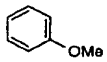
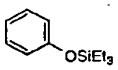
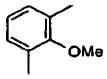
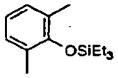
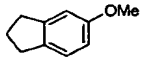
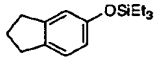
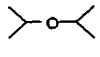
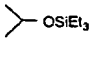
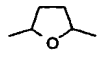
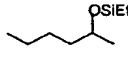
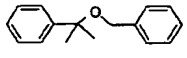
Mechanistic Studies and Discussion. The observed unusual high reactivity of primary alcohols **1a–e** (eq 1, Table 1) and ethers **4a–h** (eq 2, Table 2) toward reduction with the $HSiEt_3$/cat.-$B(C_6F_5)_3$ system seemed to be easily understood in terms of the S_N2 mechanistic pathway rather than S_N1 protocol.[15] This proposal can be examined by investigating the stereochemistry of the reduction of the chiral alcohol (e.g., (*S*)-(−)-**1i**) with deuterated silane (Scheme 3). Indeed, if the reduction proceeds through the carbenium intermediate **6** (S_N1 pathway, Scheme 3), the formation of racemic hydrocarbon **7** is unavoidable.[3] However, if the concerted mechanism is involved (transition state **8**), the formation of product **9** with complete or notable inversion of configuration at the secondary carbon center[16] should be observed (S_N2 pathway, Scheme 3). Since the abovementioned study cannot be applied to primary alcohols, we searched for a suitable secondary substrate. It was found that triethylsilyl ether of (*S*)-(−)1-phenylethanol (*S*)-(−)-**1i** could serve for this purpose. Although the secondary silyl ether **3e** did not undergo reduction with triethylsilane (Table 1, entry 10), the test experiments indicated that it could be reduced into **2d** by treatment with less bulky dimethylethylsilane. Therefore, to study the stereochemistry of the reduction, (*S*)-(−)-**3e** was prepared. The experiment on the reduction of (*S*)-(−)-**3e**

(14) Similarly, rather bulky silyl ethers of benzyl alcohol, such as TIPSOBn (**1m**), TBDPSOBn (**1n**), and TBDMSOBn (**1o**), were resistant toward reduction with $HSiEt_3/B(C_6F_5)_3$ system.

(15) Generally, the nucleophilic substitution at primary sp^3 carbon should proceed via S_N2 rather than through an S_N1 pathway. For a review, see, for example: Hartshorn, S. R. *Aliphatic Nucleophilic Substitution*; Cambridge University Press: Cambridge, 1973.

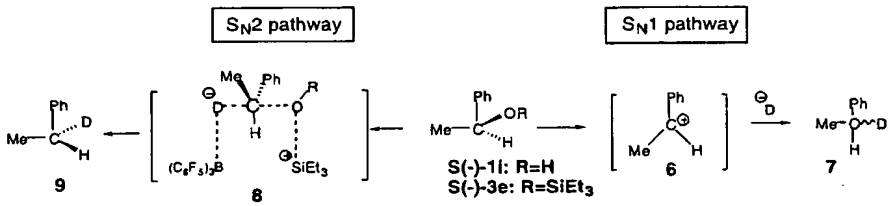
(16) For trapping of carbenium cation with chiral hydrosilane, see: Fry, J. *J. Am. Chem. Soc.* **1971**, *93*, 3558.

Table 2. Cleavage and/or Reduction of Ethers 4 with $HSiEt_3$/Cat.-$B(C_6F_5)_3$ System[a]

Entry	Ether 4		$HSiEt_3$ (eq)	Products (Isolated Yield, %)	
1	$(n\text{-}C_{16}H_{33})_2O$	(a)	1.1	$n\text{-}C_{16}H_{34}$ (**2a**) (98)	$n\text{-}C_{16}H_{33}OSiEt_3$ (**3a**) (98)
2	//		3.0		2 × **2a** (>95)
3		(b)	1.1	 (**2e**) (77)[c]	 (**3h**) (93)[b]
4	//		3.0		2 × **2e** (86)[b]
5		(c)	1.1		(**3i**) (96)
6	//		3.0		(**2h**) (97)[b]
7		(d)	//		(**2i**) (78)[b]
8		(e)	1.1		(**3j**) (>99)
9		(f)	1.1		(**3b**) (>99)
10		(g)	1.1		(**3k**) (>99)
11		(h)	1.1		(**3l**) (96)
12		(i)	3.0		(**5a**) (79)[b,c]
13		(j)	//		(**3m**) (>95)[b]
14		(k)	//		(**3n**) (97)
15		(l)	//	no reaction, recovery of **4** l 97%	

[a] All reactions were carried in CH_2Cl_2. For more detailed reaction conditions, see the Experimental Section. [b] NMR yield. [c] Yields of alcohols **5** after TBAF deprotection of the corresponding alkoxysilanes **3**.

Scheme 3. Classical S_N1 and S_N2 Pathways for the Reduction of Alcohols with LA–$HSiEt_3$ System

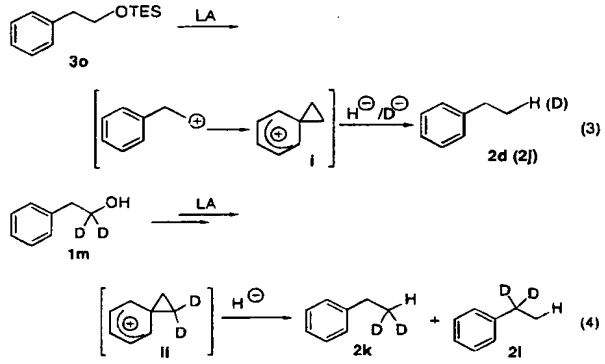


with $DSiEtMe_2/B(C_6F_5)_3$[17] in pentane revealed substantial inversion of its configuration (41% ee of (*R*)-(−)-phenylethane-1-*d* (**9**) was obtained,[18] Scheme 3). However, in slightly more polar solvent, dichloromethane, the reduction of (*S*)-(−)-**3e** produced nearly racemic **7** (2% ee, inversion). The last result is in agreement with known data, where 2% ee (retention) was observed in the reduction of the same secondary alcohol (*S*)-(−)-**1i** under the traditional method: $HSiEt_3$–stoichiometric amounts

(17) The isotopically homogeneous $DSiEtMe_2$ was prepared under the phase-transfer conditions, see: (a) Gevorgyan, V.; Ignatovich, L.; Lukevics, E. *J. Organomet. Chem.* **1985**, *284*, C31. (b) Liepins, E.; Gevorgyan, V.; Lukevics, E. *J. Magn. Reson.* **1989**, *85*, 170.

(18) On absolute configuration of enantiomerically pure deuterated phenylethanes, see: Elsenbaumer, R. L.; Mosher, H. S. *J. Org. Chem.* **1979**, *44*, 600.

of BF_3(gaseous).[19] Intrigued by the contradictory results of stereochemistry on the reduction of secondary substrate (*S*)-(−)-**3e**, we were eager to learn about the mechanism for the reduction of primary substrates. The study of kinetic hydrogen/deuterium isotope effect in the reduction of primary alcohols could give an important missing information on this matter.[20] Provided that the concerted mechanism with certain degrees of symmetry (traditional S_N2 pathway, Scheme 2) is responsible for the reduction of primary substrates, then the substantial primary isotope effect should be observed.[20] This effect will occur because the transition of deuteride from the reagent system to the electrophilic carbon center will take place at the rate-determining step.[20] Otherwise, if the reduction of primary substrates proceeds via the carbenium intermediate **6**, the deuteride transfer would not be a rate determining step,[21] consequently no notable isotope effect should be detected (Scheme 3). For the measurement of the primary kinetic isotope effect, we chose the reduction of triethylsilyl ether of phenylethanol **3o**[22] with 1:1 mixture of $HSiEt_3$ and $DSiEt_3$ in the presence of 10 mol % of $B(C_6F_5)_3$. These studies revealed negligible primary hydrogen/deuterium isotope effect (1.11 ± 0.03, and 0.97 ±.0.03 for two series of experiments), thus confirming the classical S_N1 type reaction pathway for the reduction of primary alcohols and ethers (Scheme 3). It is reasonable to propose that the reduction of **3o** proceeds via the well-known[23] phenonium cation **i** which leads to a 1:1 mixture of **2d** and **2j** (eq 3). This pathway can be easily justified by reduction of 1,1-dideuteriophenethyl alcohol **1m** (eq 4). Indeed, if the



phenonium ion **ii** is the true intermediate in the reduction of **1m**, then the formation of nearly equimolar mixture of **2k** and **2l**[24] is unavoidable[25] (eq 4). Accordingly, the deuterated alcohol **1m** was prepared[26] and subjected to the reduction with $HSiEt_3$ under the typical reaction conditions. In contrast to expectations, minor deuterium scrambling was observed. A 90:10 mixture of **2k** and **2l** was obtained, thus ruling out an involvment of the **ii** as a major intermediate in the mentioned transformation. Puzzled by the confrontational results obtained from the stereochemical and isotope effect studies, we conducted kinetic investigations on the reduction of phenylethanol **1d** with 3 equivalents of $HSiEt_3$ in the presence of 10 mol % of $B(C_6F_5)_3$ catalyst. The plot of the reaction coordinates vs time is presented in Figure 1. It became clear that the reduction of the alcohol **1d** proceeded in two steps. At the first step, **1d** underwent fast dehydrocondensation[27] with hydrosilane to produce the silyl ether **3o**. Thus, after only 1 min, the reaction mixture consisted of 78% of **3o** and 22% of **1d**, whereas in two minutes the transformation **1d** → **3o** was almost quantitative (Figure 1). The second step, reduction of the silyl ether **3o**, appeared to be dramatically slower than the first step and it took more than 8 h to complete the formation of the hydrocarbon **2d** (Figure 1).

Based on the above-mentioned stereochemical, kinetic, and isotope effect studies, we propose the following mechanistic rationale for the observed unusual reduction of alcohols and ethers in the presence of $HSiEt_3$/cat.-$B(C_6F_5)_3$ system (Schemes 4 and 5). The plausible mechanisms for the silylation of alcohols and for the reduction of particular alcohols are depicted in the Scheme 4. The reduction of diphenylmethanol (**1k**) and triphenylmethanol (**1l**), the alcohols possessing strong cation-stabilizing groups, could be explained in terms of the classical (path A) or the modified (path B) S_N1 pathways (Scheme 4). Reversible interaction of **10** with **1k** or **1l** would form an oxonium complex **11**, which would be transformed into the carbenium intermediate **12**. The latter would react with hydrosilane **13** to produce diphenylmethane (**2f**) or triphenylmethane (**2g**) and regenerate the catalyst **10** (path A, Scheme 4). According to an alternative mechanism (path B, Scheme 4), the reversible interaction of **10** with **13** would produce an ate complex **15**. The silicenium cation of **15**[28] could serve as a new Lewis acid that would coordinate to **1** to form the oxonium complex **16**,[29,30] which via the carbenium intermediate **17** would produce hydrocarbons **2f** or **2g** and would regenerate **10**. It is hard to distinguish between these two possible S_N1 pathways (paths A and B), since both of them reasonably explain the formation of the same reaction products, the hydrocarbons **2f** or **2g** and the byproduct silanol **14**[31] (Scheme 4). In the case of other alcohols, which do not possess any strong cation-stabilizing groups, the oxonium complex **16** does not transform into the carbenium intermediate **17**, instead it collapses via the dehydrocondensation process into the silyl ether **3**,[9] boron catalyst **10**, and dihydrogen[27] (path C, Scheme 4). Accordingly, in the

(19) Smonou, I.; Orfanopoulos, M. *Tetrahedron Lett.* **1988**, *29*, 5793.
(20) For a discussion on interpretation of kinetic and product isotope effects at the rate-determining step in the ene reaction, see, for example: (a) Douglas, Z. S.; Beak, P. *J. Org. Chem.* **1987**, *52*, 3938. (b) For investigation of kinetic hydrogen/deuterium primary isotope effect in the reduction of alcohols with hydro- and deuteriosilanes in the presence of stoichiometric amount of BF_3, see ref 19.
(21) For kinetic studies on hydride transfer from hydrosilanes to carbenium ions, see: Mayr, H.; Basso, N.; Hagen, G. *J. Am. Chem. Soc.* **1992**, *114*, 3060.
(22) We used silyl ether **3k** for investigation of isotope effect since the reduction of silyl ethers seems to be the slowest step in the overall transformation: alcohol → hydrocarbon (see Figure).
(23) For earlier reports on phenonium ions, see: (a) Cram D. J. *J. Am. Chem. Soc.* **1949**, *71*, 3863. (b) Cram D. J.; Davis R. *J. Am. Chem. Soc.* **1949**, *71*, 3875. (c) Cram D. J. *J. Am. Chem. Soc.* **1964**, *86*, 3764.
(24) We assume that $k_\Delta \gg k_S$ and that the secondary isotopic effect is negligible.
(25) Saunders W. H.; Asperger S.; Edison D. H. *J. Am. Chem. Soc.* **1958**, *80*, 2421.
(26) Wong, C. W.; Hamilton J. T. G.; O'Hagan, D.; Robins, R. J *Chem. Commun.* **1998**, 1045.
(27) Vigorous hydrogen emission was observed.
(28) We do not postulate an involvement of *free* silicenium cation in the proposed mechanism.
(29) Involvement of such ate-complexes in the dehydrocondensation of alcohols,[9] as well as in the reduction of carbonyl group equivalents,[30] have been recently unambiguously demonstrated.
(30) Parks, D. J.; Blackwell J. M.; Piers W. E. *J. Org. Chem.* **2000**, *65*, 3090.
(31) Formation of **14** was confirmed by GC−MS analyses of the crude reaction mixtures.

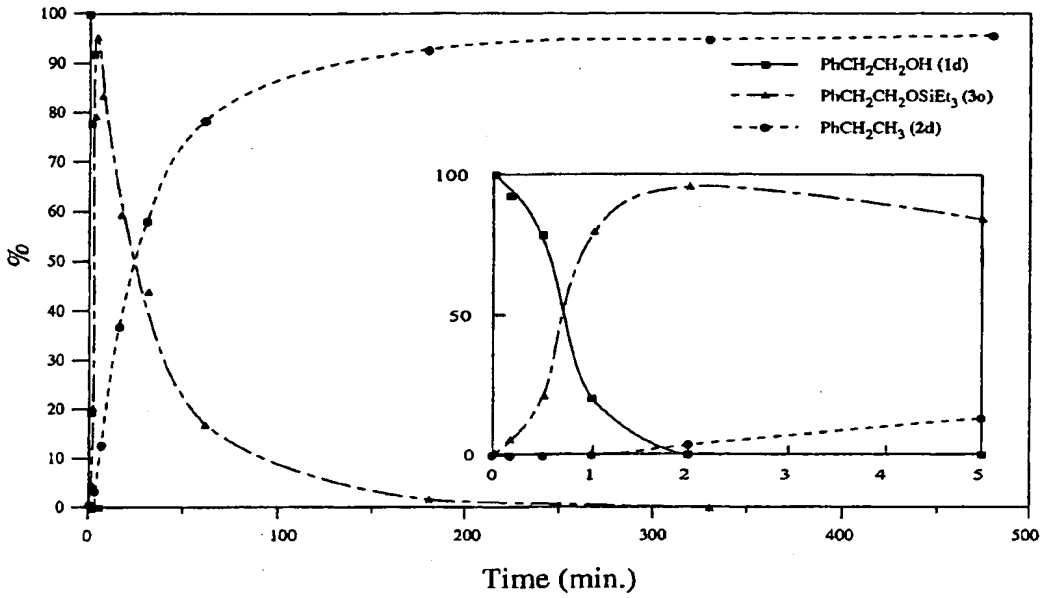
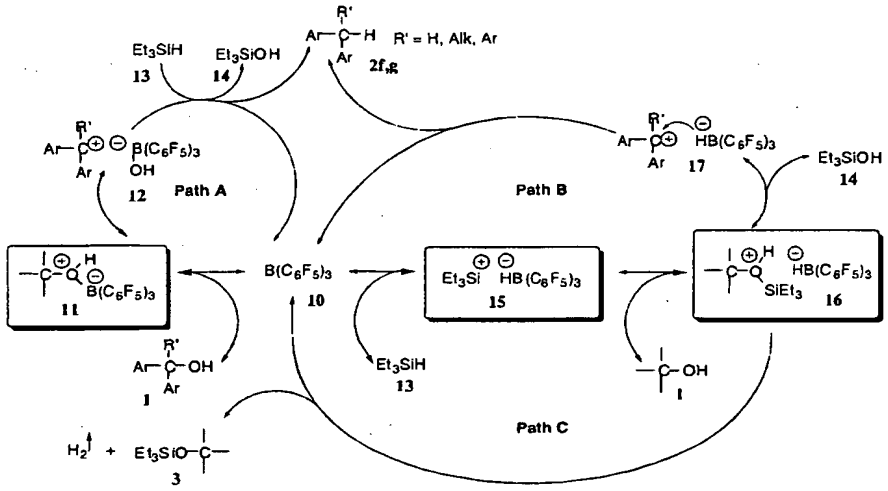


Figure 1. Reaction coordinates on reduction of **1d** with $HSiEt_3$/cat.-$B(C_6F_5)_3$ system.

Scheme 4. Proposed Mechanism for the Reduction of 1k,l and Silylation of 1a–j with 1 Equiv of Et_3SiH



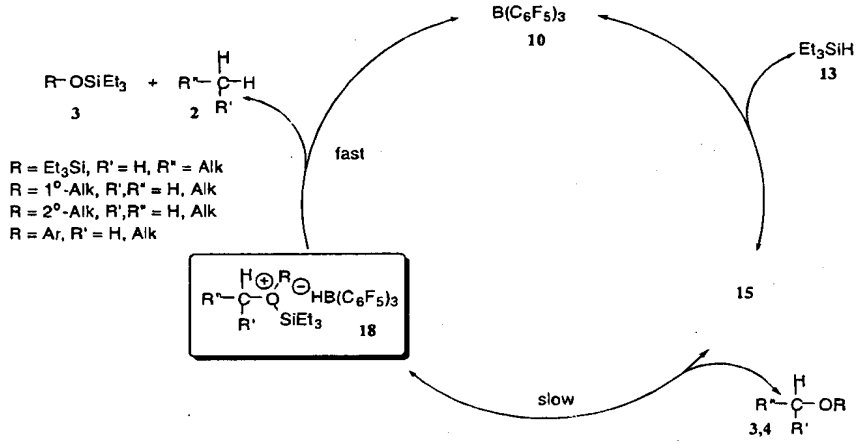
reduction of the "regular" alcohols, the first equivalent of hydrosilane is completely consumed for the formation of silyl ethers (entry 1, Table 1; Figure 1; path C, Scheme 4).

We propose that the ate-complex **15** is responsible for the reduction of silyl and alkyl ethers (Scheme 5). The silicenium cation of the ate-complex **15** would reversibly coordinate to the oxygen of silyl ether **3** (or alkyl ether **4**) to form an oxonium complex **18**, which would produce the reaction product, hydrocarbon **2**, siloxane (or silyl ether **3**) and would regenerate **10** (Scheme 5). The hydride transfer step **18** → **2** should be a fast step, as it was supported by the negligible kinetic hydrogen/deuterium isotope effect in the reduction of **3o** (see the text above). In contrast, the reversible coordination of **15** to **3** to form **18** seems to be the slowest step among the overall reduction process and completely sterically controlled. This is the key step for understanding the unusual reactivity order of primary, secondary and tertiary alcohols and ethers toward reduction. Thus, only less hindered triethylsilyl ethers **3** derived from the primary alcohols **1a–e** (Table 1, entries 2–6; Figure 1)[32] and primary ethers **4a–e** (Table 2, entries 2–8) enabled to undergo the reduction. In contrast, the triethylsilyl ethers, obtained from more bulky secondary[33] or tertiary alcohols and ethers,[33] exhibited no detectable reduction under similar reduction conditions (Table 1, entries 8–11; Table 2, entries 13–14). Reasons for the observed notable inversion of configuration of the secondary silyl ether (*S*)-(−)-**3e** (Scheme 3 and text above) are not clearly understood. It is hypothesized that (*S*)-(−)-**3e** being a border-

(32) Test experiments revealed that primary triethylsilyl ethers underwent reduction into the corresponding hydrocarbons **2**.

(33) Control experiments showed that secondary and tertiary triethylsilyl ethers in contrast to primary ones[32] did not undergo reduction with excess amounts of $HSiEt_3$.

Scheme 5. Proposed Mechanism for the Reductive Cleavage of Silyl–Alkyl, Aryl–Alkyl, and Alkyl–Alkyl Ethers



line substrate between simple alkyl alcohols and **1k,l** undergoes reduction via both intermediate **18** (Scheme 5) and some free carbenium intermediate, similar to **12** or **17** (Scheme 4).

In conclusion, we have developed a novel, effective, nontraditional method for reduction of primary alcohols and ethers and for deprotection of aryl alkyl ethers with hydrosilanes in the presence of catalytic amounts of $B(C_6F_5)_3$. The reactivity order for the reduction of primary, secondary and tertiary susbstrates (Scheme 2) is reverse to that observed in the classical reduction protocols (Scheme 1).[3,4] We believe that the present novel methodology will serve as a useful tool in synthetic organic chemistry, complementary to existing methods.

Experimental Section

General Information. All manipulations were conducted under an argon atmosphere using standard Schlenk techniques. Anhydrous solvents were purchased from Aldrich. Tertiary alcohol **1k**,[34] primary ether **4a**,[35] and tertiary ether **4l**[36] were prepared according to the standard procedures. All other compounds used were commercially available and purchased from Aldrich. Products **3b**,[37] **3d**,[38] **3e**,[39] **3h**,[40] **3i**,[41] and **3m**[42] as well as **4l** are known compounds and their analytical data were in agreement with literature data. The spectral data of new compounds **3a,c,j–l,n** are provided below. All other reaction products are commercially available compounds and their analytical data were in perfect agreement with the authentic samples.

$B(C_6F_5)_3$-Catalyzed Reduction of Alcohols and Ethers with $HSiEt_3$ (General Procedure). $HSiEt_3$ was added under an argon atmosphere to a mixture of $B(C_6F_5)_3$ (5 mol %) and alcohol **1** or ether **4** (1 mmol) in hexane or CH_2Cl_2 (1 mL). After being stirred for 20 h at room temperature, the reaction mixture was quenched by addition of triethylamine (0.05 mL), filtered through Celite, and concentrated. After the addition of appropriate internal standard (CH_2Br_2 or CH_3CCl_3 for NMR or *n*-pentadecane for GC), the mixture was analyzed by capillary GC or NMR. In the case of low bp products, the reaction mixture was analyzed by ^1H NMR without concentration. Isolated yields were determined after preparative column chromatography on silica gel.

Kinetic Isotope Effect Studies (Reduction of 3o). A mixture of $HSiEt_3$ and $DSiEt_3$ was added at once to a stirred solution of $B(C_6F_5)_3$ (10 mol %) and **3o** (1 mmol) in anhydrous hexane (1 mL) under an argon atmosphere. After stirring for 20 h at room temperature, the reaction mixture was quenched with triethylamine (0.05 mL), filtered through Celite, and concentrated. The ratios **2d/2j** were determined by ^1H NMR analyses. The isotope effects were found as 1.11 ± 0.03 and 0.97 ± 0.03 for two series of experiments with the following ratios **3o**/$HSiEt_3$/$DSiEt_3$ = 1.0:1.5:1.5 and 1.0:0.5:0.5, respectively.[43]

Stereochemical Studies on the Reduction of (*S*)-(−)-3e. $EtMe_2SiD$ (15 mmol) was added dropwise to the stirred mixture of (*S*)-(−)-**3e** (10 mmol), $B(C_6F_5)_3$ (5 mol %), and anhydrous solvent (0.5 M). The reaction mixture was stirred for 20 h at room temperature, quenched with isopropylamine (0.5 mL), and filtered through a short column of Silica gel (eluent: dichloromethane). Eluate was concentrated under ambient pressure, and the residue was purified by column chromatography on silica gel (eluent: pentane). Combined fractions containing 1-deuterioethylbenzene (**7** or **9**) were concentrated under an ambient pressure. The resulting concentrate of **7** or **9** was used for $[\alpha]^{20}_D$ determination. Exact concentration of ethylbenzene-*d* (c = 30–50) was determined by ^1H NMR using CH_2Br_2 as an internal standard. The following stereochemical results were obtained, for the reduction in pentane: $[\alpha]^{20}_D = -0.356°$ (c = 50, pentane), ee = 44% and for dichloromethane: $[\alpha]^{20}_D = -0.016°$ (c = 30, pentane), ee = 2%.

3a: ^1H NMR ($CDCl_3$, 200.13 MHz) δ 3.59 (t, J = 6.6 Hz, 2H), 1.52 (m, 2H), 1.26 (m, 26H), 0.96 (t, J = 8.0 Hz, 9H), 0.88 (t, J = 6.8 Hz, 3H), 0.59 (q, J = 8.0 Hz, 6H); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ 62.9, 32.8, 31.8, 29.6, 29.4, 29.3, 25.7, 22.6, 14.0, 6.6, 4.3; GC/MS *m/z* 355 ($M^+ - 1$, <1), 327 (100).

3c: ^1H NMR ($CDCl_3$, 400.13 MHz) δ 3.76 (m 1H), 1.26 (m, 26H), 1.12 (d, J = 6.3 Hz, 3H), 0.96 (t, J = 7.9 Hz, 9H), 0.88

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(42) Lorenz C.; Schubert U. *Chem. Ber.* **1995**, *128*, 1267. See also ref 40a.

(43) For the measurement and calculation of k_H/k_D, see, for example: Beak, P.; Berger, K. R. *J. Am. Chem. Soc.* **1980**, *102*, 3848. See also ref 19.

(t, J = 6.7 Hz, 3H), 0.59 (q, J = 7.9 Hz, 6H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 68.4, 39.8, 31.9, 30.0, 29.3, 25.8, 23.7, 22.6, 14.0, 6.8, 4.9; GC/MS *m/z* 355 ($M^+ - 1$, <1), 327 (100).

3f: ^{1}H NMR ($CDCl_3$, 500.13 MHz) δ 7.29 (m 2H), 7.24 (m 3H), 2.76 (s 2H), 1.24 (s 6H), 0.95 (t, J = 7.9 Hz, 9H), 0.59 (q, J = 7.9 Hz, 6H); ^{13}C NMR (125.75 MHz, $CDCl_3$) δ 139.3, 131.2, 127.9, 126.3, 74.0, 51.7, 30.1, 7.5, 7.2; GC/MS *m/z* 249 ($M^+ -$ 15, 3), 173 (100).

3j: ^{1}H NMR ($CDCl_3$, 400.13 MHz) δ 7.19 (dd, J = 7.3, 1.6 Hz, 1H), 7.10 (td, J = 7.7, 1.6 Hz, 1H), 6.93 (td, J = 7.3, 0.9 Hz, 1H), 6.82 (dd, J = 7.7, 0.9 Hz, 1H), 2.86 (q, J = 7.5 Hz, 2H), 1.24 (t, J = 7.5 Hz, 3H), 1.06 (t, J = 7.9 Hz, 9H), 0.82 (q, J = 7.8 Hz, 6H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 153.4, 134.4, 129.0, 126.4, 120.8, 118.0, 23.5, 14.0, 6.5, 5.2; GC/MS 236 (M^+, 48), 207 (100).

3k: ^{1}H NMR ($CDCl_3$, 400.13 MHz) δ 7.00 (d, J = 7.4 Hz, 2H), 6.82 (t, J = 7.5 Hz, 1H), 2.27 (s, 6H), 1.03 (t, J = 7.8 Hz, 9H), 0.81 (q, J = 7.9 Hz, 6H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 152.8, 128.4, 128.2, 121.1, 17.5, 6.8, 5.8; GC/MS 236 (M^+, 45), 207 (100).

3l: ^{1}H NMR ($CDCl_3$, 500.13 MHz) δ 7.08 (d, J = 8.0 Hz, 1H), 6.77 (d, J = 2.2 Hz, 1H), 6.67 (dd, J = 8.0, 2.2 Hz, 1H), 2.91 (t, J = 7.4 Hz, 2H), 2.87 (t, J = 7.4 Hz, 2H), 2.10 (ps-quintet, J = 7.4 Hz, 2H), 1.05 (t, J = 7.9 Hz, 9H), 0.78 (t, J = 7.9 Hz, 6H); ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 154.5, 146.0, 137.1, 125.0, 118.0, 116.3, 33.5, 32.5, 26.2, 7.1, 5.4; GC/MS *m/z* 248 (M^+, 56), 219 (100).

3n: ^{1}H NMR ($CDCl_3$, 400.13 MHz) δ 3.77 (m, 1H), 1.29 (m, 6H), 1.12 (d, J = 6.2 Hz, 3H), 0.96 (t, J = 7.9 Hz, 9H), 0.89 (t, J = 6.9 Hz, 3H), 0.59 (q, J = 7.9 Hz, 6H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 68.3, 39.4, 27.9, 23.7, 22.7, 14.0, 6.8, 4.8; GC/MS *m/z* 215 ($M^+ - 1$, <1), 103 (100).

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Synthesis and Structure−Activity Relationship of Novel, Highly Potent Metharyl and Methcycloalkyl Cyclooxygenase-2 (COX-2) Selective Inhibitors

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A novel series of benzo-1,3-dioxolane metharyl derivatives was synthesized and evaluated for cyclooxygenase-2 (COX-2) and cyclooxygenase-1 (COX-1) inhibition in human whole blood (HWB). In the present study, structure−activity relationships (SAR) in the metharyl analogues were investigated. The spacer group and substitutions in the spacer group were found to be quite important for potent COX-2 inhibition. Compounds in which a methylene group (**8a−c**), carbonyl group (**12a−c**), or methylidene group (**7a−c**) connected cycloalkyl groups to the central benzo-1,3-dioxolane template were found to be potent and selective COX-2 inhibitors. Aryl-substituted compounds linked to the central ring by either a methylene or a carbonyl spacer resulted in potent, highly selective COX-2 inhibitors. In this series of substituted-(2*H*-benzo-[3,4-*d*]1,3-dioxolan-5-yl))-1-(methylsulfonyl)benzene compounds, SAR studies demonstrated that substitution at the 3-position of the aryl group optimized COX-2 selectivity and potency, whereas substitution at the 4-position attenuated COX-2 inhibition. Mono- or difluoro substitution at meta position(s), as in **22c** and **22h**, was advantageous for both in vitro COX-2 potency and selectivity (e.g., COX-2 IC_{50} for **22c** = 1 μM and COX-1 IC_{50} for **22c** = 20 μM in HWB assay). Several novel compounds in the (2*H*-benzo[3,4-*d*]1,3-dioxolan-5-yl))-1-(methylsulfonyl)benzene series, as shown in structures **7c**, **8a**, **12a**, **21c**, **22c**, **22e**, and **22h**, selectively inhibited COX-2 activity by 40−50% at a test concentration of 1 μM in an in vitro HWB assay.

Introduction

Cyclooxygenases (COXs) and lipoxygenases (LOXs) are key enzymes in arachidonic acid (AA) metabolism. Eicosanoid mediators derived from COX and LOX pathways profoundly influence the development and progression of several inflammatory diseases. Prostaglandins (PGs) produced by COXs play physiological and pathophysiological roles in inflammation and in nociceptive transmission. COX exists in two isoforms: COX-1 and COX-2. Both COX isoforms metabolize AA to PGH_2, the common substrate for thromboxane-A_2 (TXA_2), prostacyclin (PGI_2), and prostaglandin-E_2 (PGE_2) synthesis. TXA_2, PGI_2, and PGE_2 play important roles in the maintenance of cardiovascular homeostasis. TXA_2 is primarily synthesized by COX-1 in platelets. COX-1-derived constitutive PGs are cytoprotective in the gastrointestinal (GI) tract. Inducible COX-2 is expressed at sites of inflammation by monocytes and macrophages and plays a key role in mediating the inflammatory process.[1] PGE_2 and leukotriene-B_4 (LTB_4) are the predominant eicosanoid inflammatory mediators.

Under basal physiological conditions, LOX-derived leukotrienes (LTs) are not produced by the GI mucosa in appreciable quantities. However, LTs are generated under inflammatory conditions[2] in the GI tract.[3] LT production during COX-1 inhibition due to diversion of the substrate AA to 5-LOX may contribute to GI mucosal injury by increasing microvascular permeability. In addition, one of the mediators produced by this pathway, LTB_4, is a potent chemotactic agent[4] that exerts its biological activity via BLT-1 and recently identified BLT-2 receptors.[5,6] At the site of inflammation, increased LTB_4 production also leads to activation of proinflammatory cytokines, e.g., tissue necrosis factor-α (TNF-α) and interleukin-1β (IL-1β). After the discovery of COX-2, it has been confirmed that IL-1β-stimulated chondrocytes from normal as well as osteoarthritic human cartilage induced COX-2 expression,[7] whereas, COX-1 was not detected in either normal or osteoarthritic chondrocytes.[8] Since there is no COX-1 in chondrocytes, traditional nonselective nonsteroidal antiinflammatory drugs (NSAIDs) are effective in reducing pain in arthritis by inhibiting COX-2.

NSAIDs are widely used for reducing pain and inflammation. However, chronic NSAID use may cause serious GI side effects, such as ulceration. NSAIDs induce GI damage by multiple mechanisms and vary in ulcerogenic activity in different regions of the GI tract. Both PG-dependent and -independent factors are responsible for the NSAID gastric toxicity. PG-dependent factors include the influences of PGs on mucus−bicarbonate secretion, regulation of acid secretion, and blood flow. Since the discovery of inducible COX-2, it has been possible to separate the roles of constitutive COX-1 and inducible COX-2 isozymes. Selective inhibition of COX-2 has proved to be a useful therapeutic target.[9] As a result, pharmaceutical companies have developed and tested extensive libraries of COX-2-selective inhibitors[1,10] with the hypothesis that selective

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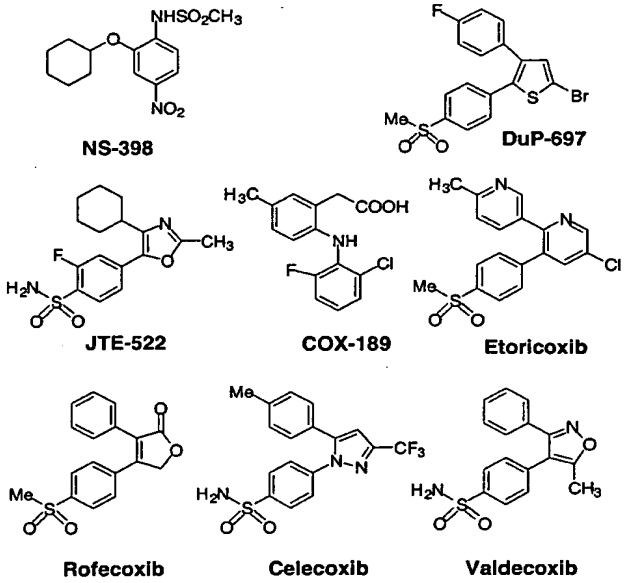
Chart 1



COX-2 inhibiton should block the prostaglandin production in inflammatory cells, while not interfering with the production of gastroprotective PGs in the GI tract by COX-1.

A number of pharmaceutical companies directed their research efforts and resources for the development of potent and selective COX-2 inhibitors. The clinical efficacy and impressive GI safety of COX-2 inhibitors resulted in the United States Food and Drug Administration (FDA) approval of two COXIBs, celecoxib and rofecoxib (Chart 1), as the first-generation, selective COX-2 inhibitors marketed for the treatment of inflammatory diseases. Specifically, for the treatment of acute pain, osteoarthritis, and rheumatoid arthritis,[11-14] they seem to be as effective as classical NSAIDs with reduced deleterious GI side effects.[15] Recently, valdecoxib received FDA approval as a COX-2 selective antiinflammatory drug,[16,17] and another COX-2 selective inhibitor, JTE-522,[18] is in a phase II clinical trial while COX-189[19] and etoricoxib are completing phase III clinical studies.

Prior to the proposal and confirmation of the COX-2 hypothesis, compounds such as NS-398 and DuP-697 demonstrated antiinflammatory activity with GI-sparing profiles in animal models.[20-22] Later, it was confirmed that DuP-697 and NS-398 preferentially inhibited COX-2 over COX-1.[23,24] These two compounds were the early lead candidates of COX-2-selective inhibitors, and especially, the central thiophene ring of DuP-697 provided a five-member ring template for the development of COX-2 inhibitors.

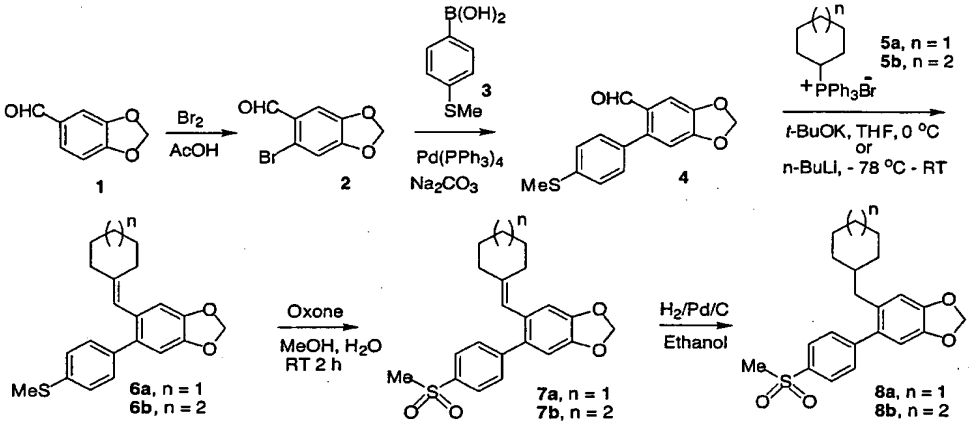
Structural biology[25,26] and X-ray crystallography[27,28] provided more useful information for the development of COX-2 inhibitors. Generally, for good COX-2 inhibitory activity and selectivity, compounds require a key pharmacophore,[29] the 4-methylsulfonylphenyl group, attached to a five-membered ring in which additional vicinal aryl ring substitution is present. The methyl sulfone group may be replaced by a sulfonamide, whereas the COX-2 inhibitory potency can be tuned-up by various substitutions on the other aryl ring. By utilizing a variety of five-member ring templates to give *o*-diaryl-substituted compounds with rigid conformation, many COX-2 selective inhibitors have been identified. Several interesting five-member ring templates include pyrazoles,[11,30] furanones,[12] cyclopentenes,[31,32] cyclopentenones,[33] imidazoles,[34,35] isoxazoles,[17] pyrroles,[36] oxazoles,[37] oxazolones,[38] and spiroheptenes.[39] The three FDA approved drugs, e.g., celecoxib, rofecoxib, and valdecoxib, are representative examples of the diaryl-substituted pyrazole, diaryl-substituted furanone, and diaryl-substituted isoxazole series, respectively. The five-member rings have also been replaced by six-member aryl[40] and heteroaryl rings.[41] Etoricoxib is an example of a diaryl-substituted pyridine COX-2 selective inhibitor.[41,42] A few bicyclic systems have been explored as central templates for the development of COX-2-selective inhibitors. Among the bicyclic systems, diaryl-substituted indanones[43] and pyrazolopyrimidines[44] have been reported. Classical NSAID templates have also been used to convert a COX-1-selective compound into a COX-2 selective inhibitor by slight modification. For example, conversion of indomethacin into various amide derivatives has generated COX-2 selective inhibitors.[45] On the basis of the COX-1 and COX-2 crystal structures, rationally designed COX-2 selectivity was achieved in flurbiprofen analogues.[46] Molecular modeling experiments also provide a better understanding of COX-2 enzyme–inhibitor interactions and possible guidelines to predict structure–activity relationships for novel COX-2 inhibitor design.[47-49]

As a part of our ongoing program to explore novel classes of COX-2 inhibitors, we report a new series of metharyl COX-2 selective inhibitors. In a novel approach to ortho-substituted aryl or cycloalkyl COX-2-selective inhibitors, we determined the effect of incorporating a spacer group between the cycloalkyl, aryl, or heteroaryl ring and central ring. Primarily, we have used a one-carbon spacer between the central benzo-1,3-dioxolane ring (template) and the aryl, heteroaryl, or cycloalkyl rings; therefore, as a generic name we refer to these compounds as the metharyl and the methcycloalkyl series compounds. In the present study, benzo-1,3-dioxolane was selected as the central ring for the SAR study in view of the easier access to substituent variation. Herein, we report that analogues of the vicinal-substituted benzo-1,3-dioxolanes are potent COX-2 inhibitors and a spacer group between the central ring and the cycloalkyl-, aryl- or heteroaryl group plays an important role in COX-2 inhibitory potency. Details of the synthetic studies and structure–activity relationships among these compounds are presented.

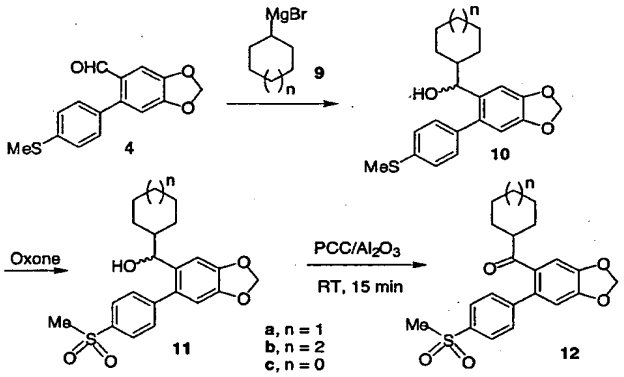
Chemistry

Our initial strategy was to investigate 1-(6-(cycloalkylmethyl)(2*H*-benzo[3,4-*d*]1,3-dioxolen-5-yl))-4-(methylsulfonyl)benzene analogues such as **8a** and **8b** in an effort to determine if incorporating a methylene spacer group between the central benzo-1,3-dioxolane ring and the cycloalkyl ring might improve in vitro COX-2 inhibitory potency. Synthesis of a series of (cycloalkylmethyl)benzo-1,3-dioxolanes **8a** and **8b** was conveniently accomplished as shown in Scheme 1. The known bromopiperonal **2** was prepared by bromination of

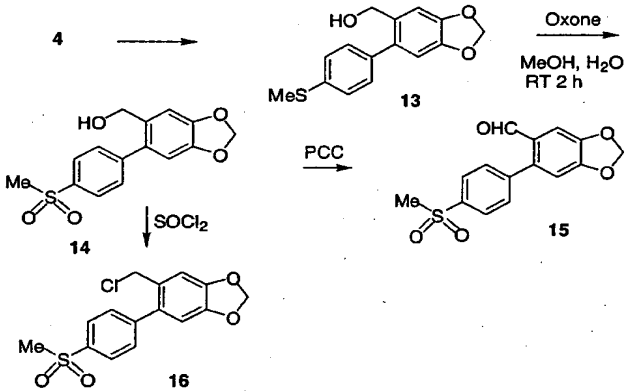
Scheme 1



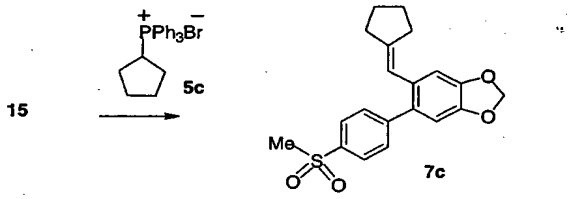
Scheme 2



Scheme 3



Scheme 4



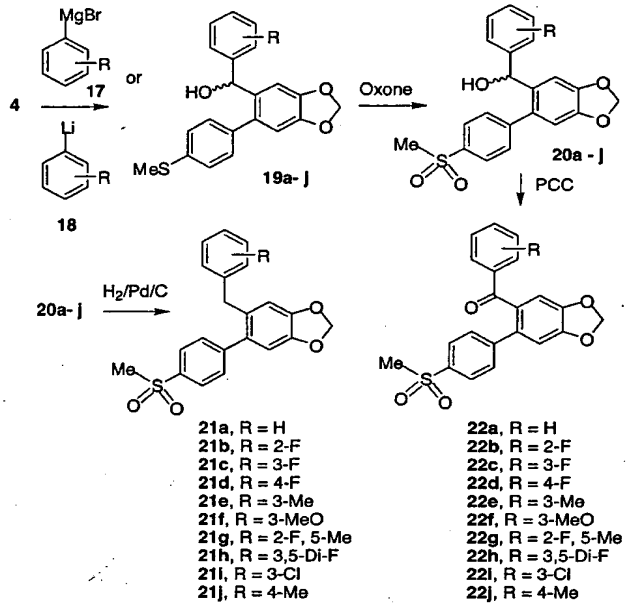
piperonal **1** using bromine in acetic acid.[50] The resulting bromoaldehyde **2** was converted to the key synthon 6-(4-methylthiophenyl)-2*H*-benzo[*d*]1,3-dioxolane-5-carbaldehyde **4** in high yield by Suzuki cross-coupling with 4-(methylthio)phenyl boronic acid **3** using standard conditions.[51] The Wittig coupling of carbaldehyde **4** with the ylides generated from **5a** or **5b** afforded the desired tricyclic compounds **6a** or **6b** in good yields. Oxidation of methylthio compounds **6a** and **6b** with Oxone gave the corresponding methyl sulfones **7a** and **7b** in excellent yields. Hydrogenation of **7a** and **7b** using Pd/C catalyst at 25−40 psi pressure provided **8a** and **8b** in nearly quantitative yields.

The synthetic method for the preparation of **12a−c** is outlined in Scheme 2. Reaction of aldehyde **4** with appropriately substituted Grignard reagents gave tricyclic compounds **10a−c**. These compounds **10a−c** were then oxidized with Oxone to give the corresponding methyl sulfones **11a−c**. The benzylic hydroxyl groups in **11a−c** were either deoxygenated by hydrogenolysis to give **8a−c** or oxidized to give the corresponding carbonyl compounds **12a−c**.

As shown in Scheme 3, an initial focus of our strategy was to prepare appropriately substituted key synthons, e.g., (6-(4-methylsulfonyl)phenyl)-2*H*-benzo[*d*]1,3-dioxolane-5-carbaldehyde) **15**, 1-(6-(chloromethyl) (2*H*-benzo-[3,4-*d*]1,3-dioxolan-5-yl))-4-(methylsulfonyl)phenyl)-2*H*-benzene **16**, and use these intermediates in a convergent manner to prepare the planned target compounds for COX in vitro screening and SAR studies. One such example is illustrated in Scheme 4. Wittig condensation of methylsulfonyl aldehyde **15** with the ylide derived from phosphonium **5c** gave **7c** in one step.

As will be discussed below, our attention was next focused toward alternative core structures related to **21** and **22**. The syntheses of these compounds were accomplished as shown in Scheme 5. Aldehyde **4** (Scheme 1) was prepared in large quantities (200−300 g) in two steps from commercially available piperonal in 62% overall yield. Lithio derivatives **18a−j** were conveniently prepared by metal halogen exchange of the corresponding haloarenes with *n*-BuLi or *t*-BuLi at −78 °C and subsequently quenched by addition of aldehyde **4** in THF to provide alcohols **19a−j**. Alternatively, Grignard reagents **17a−j** were prepared from the corresponding haloarenes and then treated with aldehyde **4** to give **19a−j**. These compounds **19a−j** were then oxidized with Oxone to form the corresponding sulfones **20a−j**. The

Scheme 5



21a, R = H
21b, R = 2-F
21c, R = 3-F
21d, R = 4-F
21e, R = 3-Me
21f, R = 3-MeO
21g, R = 2-F, 5-Me
21h, R = 3,5-Di-F
21i, R = 3-Cl
21j, R = 4-Me

22a, R = H
22b, R = 2-F
22c, R = 3-F
22d, R = 4-F
22e, R = 3-Me
22f, R = 3-MeO
22g, R = 2-F, 5-Me
22h, R = 3,5-Di-F
22i, R = 3-Cl
22j, R = 4-Me

doubly benzylic hydroxyl groups in **20a–j** were converted to the ketones by treatment with pyridinium chlorochromate (PCC) in dichloromethane to give the desired compounds **22a–j**. Alternatively, the hydroxyl groups in **20a–j** were deoxygenated by hydrogenolysis to give **21a–j**.

Attention was also focused on preparing (pyridylmethyl)benzo-1,3-dioxolane derivatives. Benzo-1,3-dioxolane-2-, 3-, and 4-(pyridylmethyl) derivatives were synthesized from **4** utilizing the same methodology, as depicted in Scheme 4. In Scheme 6, details of the preparation of the 3-(pyridylmethyl)-substituted analogue **27** are illustrated. 3-Lithiated-pyridine **24** was prepared by metal halogen exchange of 3-bromopyridine **23** with *t*-BuLi at −78 °C, followed by quenching the 3-lithiopyridine **24** by the aldehyde **4** to give the sulfide **25**. Oxidation of sulfide **25**, with Oxone proceeded smoothly to yield methyl sulfone **26**. Deoxygenation of **26** was carried out at room temperature by treating **26** with triethylsilane in dichloromethane/TFA to give **27**.[52]

Oxidation of **26** using PCC gave the compound **28**, with a carbonyl spacer group.

Using a similar reaction sequence as that shown in Scheme 6, the methyl-substituted 2-pyridyl analogue **31**, with a carbonyl spacer group was prepared as shown in Scheme 7. However, the same methodology when used to prepare 6-(4-(methylsulfonyl)phenyl)(2*H*-benzo-[*d*]1,3-dioxolan-5-yl) 3-pyridyl ketone **36**, unexpectedly gave two products, **35** and **36** (Scheme 8). Initial metalation of 4-bromopyridine **32** gave a mixture of two lithiated species, 4-bromo-3-lithio- and 4-lithiopyridine, which upon quenching with **4** resulted in a mixture of **33** and **34**. The mixture was separated by flash column chromatography to give pure compounds **33** and **34**, each one was independently converted to the corresponding methyl sulfone, and subsequently the alcohol was oxidized to give compounds **35** and **36**, respectively.

A number of other alternative piperidinyl-substituted structures were pursued as well. The preparations of **38a–f** are illustrated in Scheme 9. Chloro compound **16** was reacted with various substituted piperidine derivatives **37** using potassium carbonate as base, giving the corresponding diaryl sulfones **38a–f** in good yields.

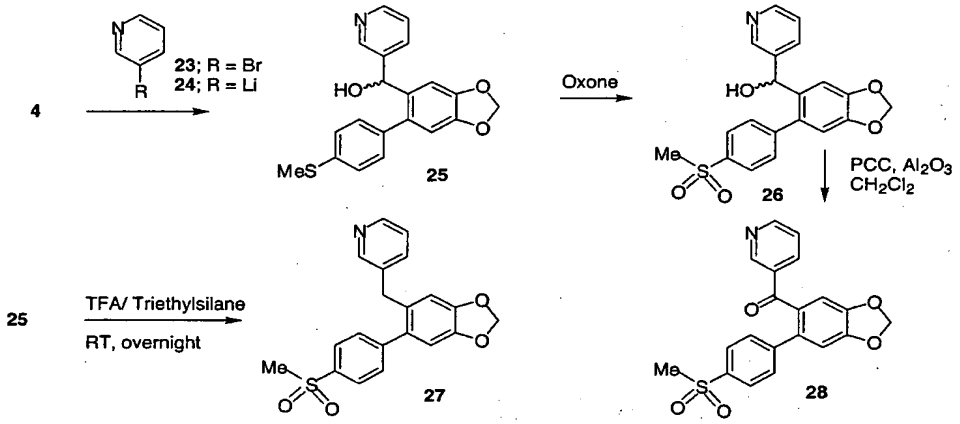
To decrease the basicity of the nitrogen in **38a**, the heterocyclic pattern of **38a** was modified. Compound **42** was synthesized by a straightforward transformation of the methylthio compound **4** as shown in Scheme 10.

An alternative approach to decrease the basicity of nitrogen in **38a** was achieved by preparing compounds as **45a,b** and **46a,b**. Carboxylic acid **43a** was prepared in two steps. It was then converted to the corresponding acid chloride **43b** and coupled with heterocycles **44a,b** to give the heterocycloalkyl-substituted benzo-1,3-dioxalane analogues **46a**, **46b**, and **45b** in which a carbonyl group spacer is introduced between the heterocyclic ring and the central benzo-1,3-dioxolane ring, as shown in Scheme 11.

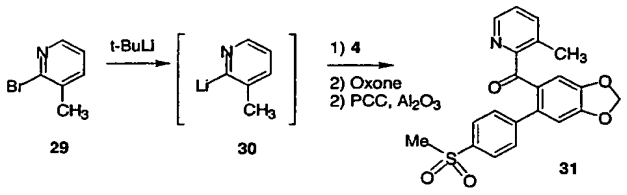
To examine the effect of sulfonamide pharmacophore on the COX-2 potency and selectivity, the methyl sulfone in **21a** was transformed into a sulfonamide to give **47** as shown in Scheme 12.

To study the effects of fluoro substitution on the phenylmethyl sulfone pharmacophore, the corresponding (fluoromethyl)phenyl sulfone **50** was prepared as

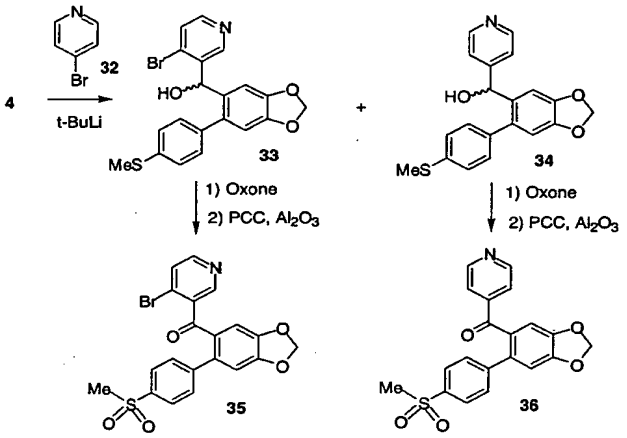
Scheme 6



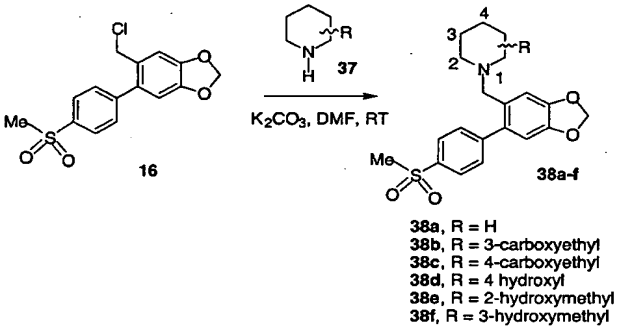
Scheme 7



Scheme 8

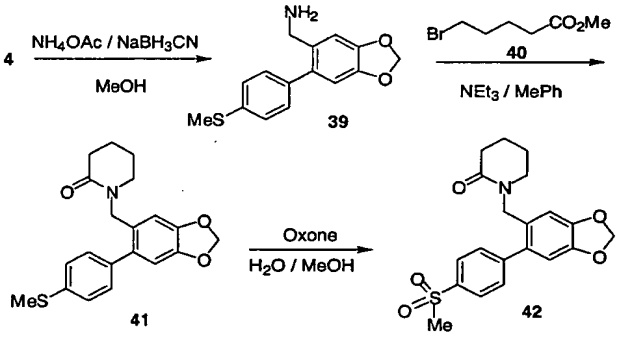


Scheme 9



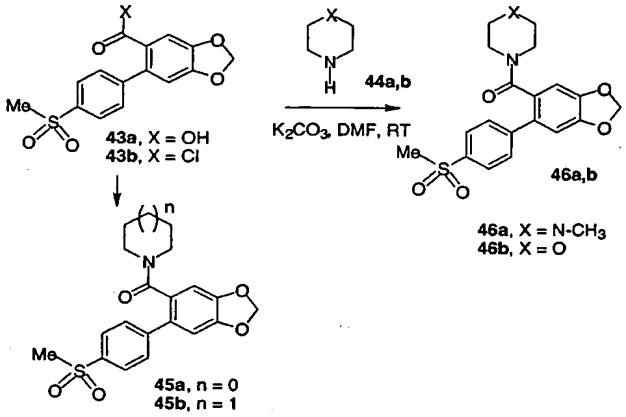
38a, R = H
38b, R = 3-carboxyethyl
38c, R = 4-carboxyethyl
38d, R = 4 hydroxyl
38e, R = 2-hydroxymethyl
38f, R = 3-hydroxymethyl

Scheme 10



shown in Scheme 13.[53] Hydroxyl compound **19a** was hydrogenated overnight at 40 psi pressure to give the deoxygenated product **49a**. Interestingly, when compound **19a** was treated with sodium borohydride in the presence of trifluoroacetic acid, the desired product **49a** was not obtained. Instead, tricyclic compound **48** was

Scheme 11

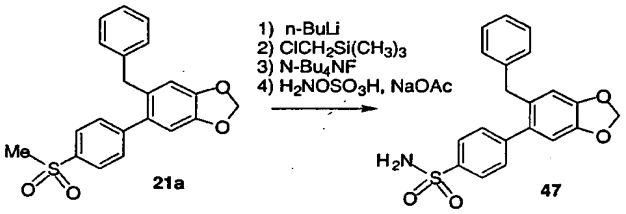


43a, X = OH
43b, X = Cl

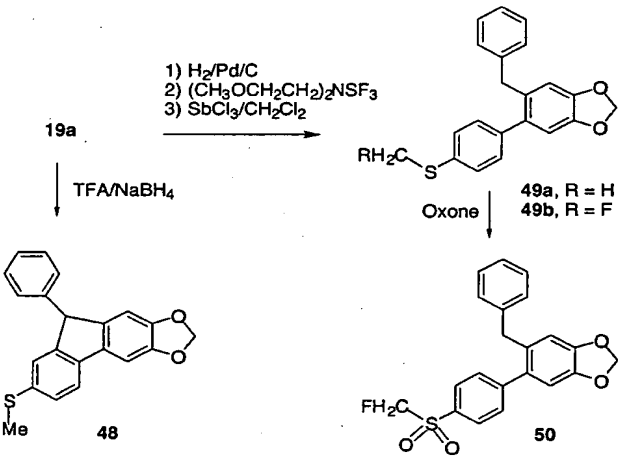
45a, n = 0
45b, n = 1

46a, X = N-CH$_3$
46b, X = O

Scheme 12



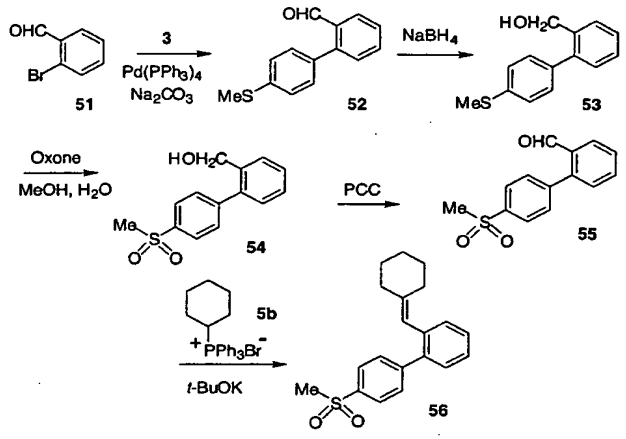
Scheme 13



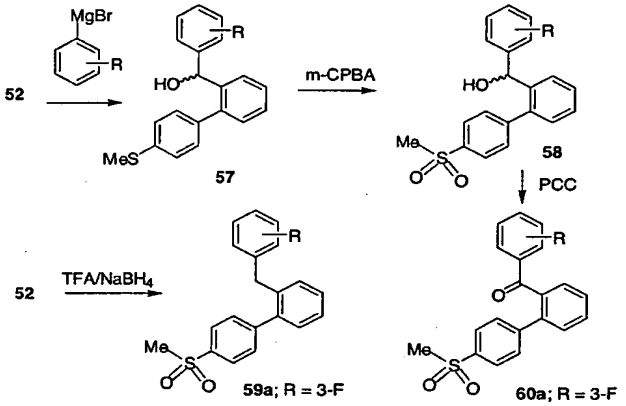
obtained in nearly quantitative yield. The formation of **48** can be rationalized on the basis of stable doubly benzylic carbocation formation followed by ring closure. Fluorination of thiomethyl group in **49a** was performed by treating **49a** with [bis(2-methoxyethyl)amino] sulfur trifluoride in the presence of a catalytic amount of $SbCl_3$ to furnish **49b**, which was subsequently oxidized with *m*-chloroperbenzoic acid to give **50**.

For studying the SAR of the dioxolane ring, compounds not containing this ring, such as **56** and **60**, were prepared. The details are outlined in Schemes 14 and 15. Compounds containing no spacer group between the central ring and the aryl ring, such as **65**, were prepared as shown in Scheme 16.[40] To study the effect of lengthening the spacer (linker) between the aryl and central ring, as in **21a**, compound **67** with a three-

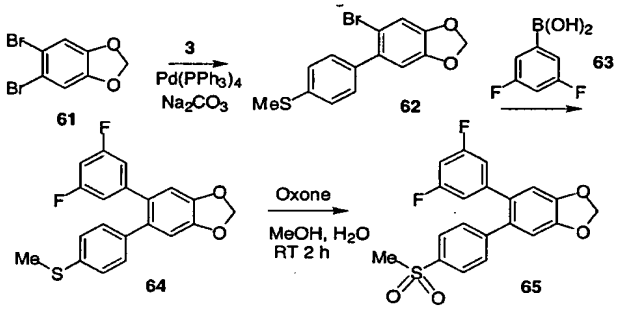
Scheme 14



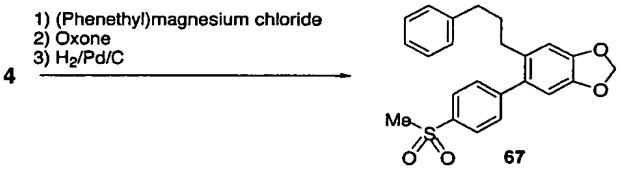
Scheme 15



Scheme 16



Scheme 17



carbon spacer group was prepared, as shown in Scheme 17. In addition, the dimethoxy compound **72** and benzo[*e*]1,4-dioxin-2-yl compound **74** were also prepared (Scheme 18).

Results and Discussion

As an initial screen to determine the in vitro COX-1 and COX-2 inhibitory activity, we evaluated compounds for their ability to inhibit recombinant human or ovine COX-1 at a 100 μM test concentration and COX-2 at both 10 and 1 μM test concentrations (Tables 1 and 2). Compounds that showed good COX-2 inhibition at 1 μM were also evaluated at various concentrations as COX-2 and COX-1 inhibitors to assess COX-2 selectivity (Table 3). Once initial lead compounds were so identified, they were evaluated in a human whole blood (HWB) assay, which takes into account the interactions of inhibitors with blood proteins and the ability of test compounds to traverse cellular membranes in a physiological setting. Eventually, all newly synthesized compounds were evaluated only in the HWB assay.

Recently, it has been reported that the bulky cyclohexyl group, as compared to the aryl group, enhances the COX-2 selectivity of JTE-522, an oxazole series COX-2 inhibitor.[18] In our initial SAR studies, we used 4-(methylsulfonylphenyl)benzo-1,3-dioxolane as a template and explored the effects of cycloalkyl groups of various sizes at the vicinal position as well as the linkage between the central ring and the cycloalkyl ring. We were gratified to find that several of the initial compounds screened in the recombinant enzyme assay were very potent, highly selective COX-2 inhibitors. Compounds **7a**, **7b**, and **8a** did not inhibit COX-1, even at 100 μM in the enzyme assay. Our studies demonstrated that, by connecting the cycloalkyl substituent to the central benzo-1,3-dioxolane template by a one-carbon spacer group, it was possible to prepare potent, selective COX-2 inhibitors. Evaluation of compounds **7a–c** and **8a–c** in the HWB assay confirmed that these compounds are potent COX-2 inhibitors; however, under these conditions some COX-1 inhibition was also detected (Table 1). Introduction of a double bond between the cycloalkyl substituent and the central ring improved the COX-2 inhibitor profile. When connected by a rigid double bond, the corresponding compounds such as **7a–c** were found to be slightly more potent COX-2 inhibitors than **8a–c** having a methylene group in the linkage. At a 10 μM concentration, **7a–c** and **8a–c** exerted substantial (75–90%) COX-2 inhibition in HWB.

SAR of Aryl-Substituted Analogues. Aryl group substitution is commonly incorporated into *o*-diaryl substituted COX-2 inhibitor design. It is well-established that *p*-methyl sulfone or sulfonamide on one of the phenyl rings is required for good COX-2 potency and selectivity. A variety of substituents could be added to the other phenyl ring to secure or enhance the COX-2 inhibitory potency. To investigate the SAR of the aryl-substituted analogues, we next focused attention on the preparation of aryl-substituted analogues of **8a**. In most of the known diaryl-substituted COX-2 inhibitors, the two rings are periplanar to the central ring. We expected that in the metharyl-substituted compound **21a** the methylene linkage that acts as a spacer between the aryl ring and the central benzo-1,3-dioxolane ring should give the molecule more flexibility to adopt a conformation suitable for the interaction at the enzyme's active site. Unsubstituted-aryl-ring compound **21a** exhibited modest COX-2 inhibitory potency ($IC_{50} = 10\ \mu M$), as well as a 6-fold COX-2/COX-1 selectivity (IC_{50} for

Scheme 18

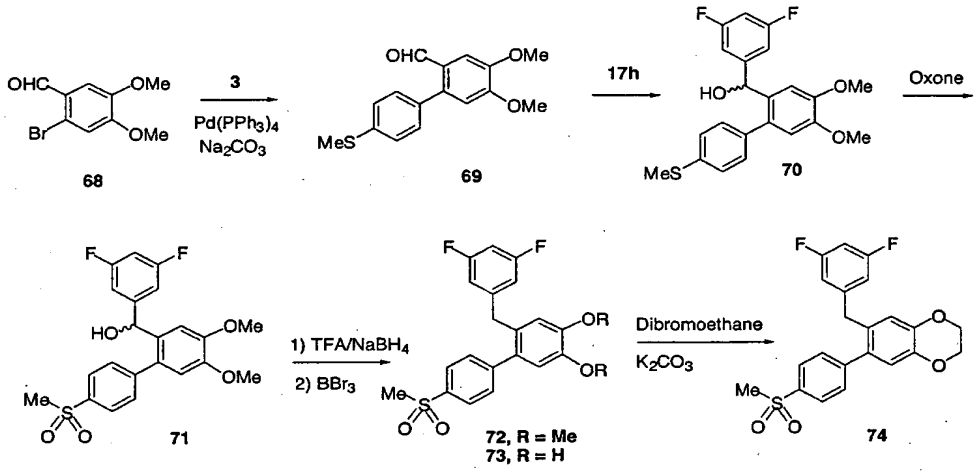
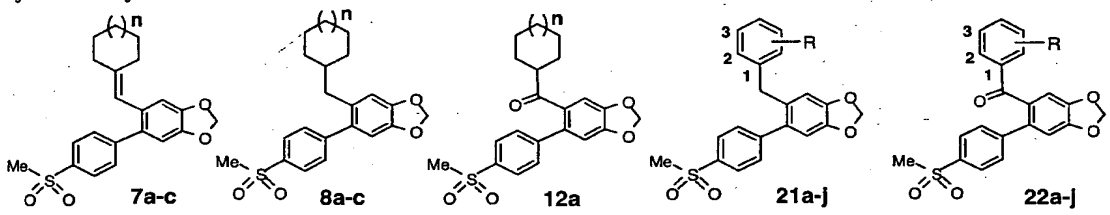


Table 1. Percent Inhibition of Recombinant COX-1 (Human or Ovine), COX-2 (Human) Enzyme Activity and Human COX-1 and COX-2 Enzyme Activity in HWB



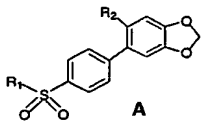
compd	substituent	recombinant[a] COX-1 (100 μM)[b]	recombinant[a] COX-2 (10 μM)[b]	recombinant[a] COX-2 (1 μM)[b]	HWB[d] COX-1 (100 μM)[b]	HWB[d] COX-2 (10 μM)[b]	HWB[d] COX-2 (1 μM)[b]
7a	n = 1	0	90	90	50	90	40
7b	n = 2	0[c]	100	100	35	90	25
7c	n = 0	80[c]	90	65	70	90	55
8a	n = 1	0	100	100	50	75	20
8b	n = 2	10[c]	100	90	40	80	25
8c	n = 0	20[c]	70	40			
12a	n = 1				55	85	40
20a		0	0	0			
21a	R = H	0	85	85	65	50	10
21b	R = 2-F				75	40	5
21c	R = 3-F				25	90	40
21d	R = 4-F	10[c]	0	10			
21e	R = 3-Me				10	40	10
21f	R = 3-MeO				35	10	0
21g	R= 2-F, 5-Me				40	50	25
21h	R = 3,5-di-F	15[c]	90	90	70	40	15
21i	R = 3-Cl				65	100	40
21j	R = 4-Me	25[c]	80	50	45	10	0
22a	R = H	0	90	10	75	65	25
22b	R = 2-F				70	95	30
22c	R = 3-F				50	95	50
22d	R = 4-F				95	5	0
22e	R = 3-Me	0[c]	40	10	95	85	40
22f	R = 3-MeO				95	75	10
22g	R = 2-F, 5-Me				90	90	25
22h	R = 3,5-di-F				50	95	50
22i	R = 3-Cl				90	100	15
22j	R = 4-Me				60	10	0
celecoxib		80	100	90	NT	100	50
rofecoxib		0	100	40	75	100	75

[a] Unless indicated otherwise, percent inhibition of recombinant human COX-1. [b] Concentration of test inhibitor. [c] Inhibition of recombinant ovine COX-1. [d] Average percent inhibition of two donors.

COX-1 = 60 μM) in HWB (Table 4). The length of the spacer between the central ring and the aryl group is also critical for COX-2 inhibition. Lengthening the spacer to three carbons, as in **67** (Table 2), resulted in the loss of COX-2 inhibitory potency.

Next we explored the effects of aryl substitution at ortho-, meta-, and para-positions on the phenyl ring of compound **21a** on COX inhibitor potency and selectivity in the HWB assay. As shown in Table 1, differences in COX-2 inhibitory potencies were observed when the aryl

Table 2. Percent Inhibition of Recombinant COX-1 (Human or Ovine), COX-2 (Human) Enzyme Activity and Human COX-1 and COX-2 Enzyme Activity in HWB



A

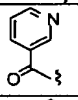
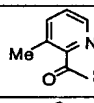
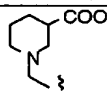
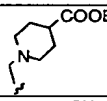
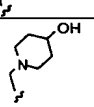
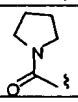
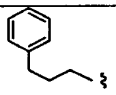
Comp. #	R_1	R_2	COX-1[a] Recomb. (100 μM)[b]	COX-2 Recomb. (10 μM)[b]	COX-2 Recomb. (1 μM)[b]	COX-1 HWB[d] (100 μM)[b]	COX-2 HWB[d] (10 μM)[b]	COX-2 HWB[d] (1 μM)[b]
27	Me		30	65	0	35	15	15
28	Me		20	20	0			
31	Me		0	10	0			
35	Me		40[c]	0	10			
38a	Me		0	30	0			
38b	Me		10	40	40			
38c	Me		0	20	20			
38d	Me		0	25	10			
38e	Me		0	30	25			
38f	Me		0	30	20			
42	Me		70	90	20	50	35	15
45a	Me		0	20	0			
45b	Me		15	40	20			
46a	Me		15	15	20			
46b	Me		10	10	35			

Table 2. (Continued)

Comp. #	R_1	R_2	COX-1[a] Recomb. (100 μM)[b]	COX-2 Recomb. (10 μM)[b]	COX-2 Recomb. (1 μM)[b]	COX-1 HWB[d] (100 μM)[b]	COX-2 HWB[d] (10 μM)[b]	COX-2 HWB[d] (1 μM)[b]
47	NH_2		90	90	85	90	0	0
50	$-CH_2F$		50[c]	50	25			
56						60	90	40
59a						35	10	0
60a						45	40	10
65						65	35	0
67	Me		10	0	15	65	35	15
72						0	15	15
74						70	40	15

[a] Unless indicated otherwise, percent inhibition of recombinant human COX-1. [b] Concentration of test inhibitor. [c] Percent inhibition of recombinant ovine COX-1. [d] Average percent inhibition of two donors.

Table 3. IC_{50} Values of Various Compounds in Recombinant COX-1 (Human), COX-2 (Human) Enzyme Assay

compd	IC_{50} (μM) COX-1	IC_{50} (μM) COX-2	COX-2/COX-1 selectivity
7a	>100 (nd[a])	0.07	>1400
7b	>100 (nd)	0.2	>500
47	25	0.05	500
celecoxib	<100	0.054	nd
rofecoxib	>100	1.0	>100

[a] nd = not determined.

Table 4. IC_{50} Values of Various Compounds and Standard COX-2 Inhibitors for COX-1 and COX-2 Enzymes in Human Blood

compd	IC_{50} (μM) COX-1	IC_{50} (μM) COX-2	COX-2/COX-1 selectivity
21a	60	10	10
22c	20	1.0	20
47	60	nd[a]	nd
celecoxib	14	1.2	11
rofecoxib	40	0.3	133

[a] nd = not determined.

ring was substituted at position 2-, 3-, or 4 with, for instance, halogen, methoxy, or methyl groups. In this bicyclic system, incorporation of substituent at the para-position of the phenyl ring had a deleterious effect on COX-2 inhibitory potency. Compounds **21j** and **22j**, with a 4-Me substituent, were not COX-2 inhibitors at a 1 μM test concentration in HWB. It is important to note the differences in COX-2 potency of **21j** in the enzyme assay and in HWB. In the enzyme assay **21j** exhibited 50% inhibition at 1 μM test concentration, whereas at this concentration it did not exhibit COX-2 inhibition in HWB. Surprisingly, 4-fluoro substitution in compound **21d** abrogated the COX-2 inhibitory activity. In general, 4-fluoro substitution on the aryl ring increases COX-2 potency. The active site of COX-2 offers more accessible space than that of COX-1, due to substitution of the amino acid valine for isoleucine at position 523.[25,26] The valine substitution opens up additional space that has proven to be important for the binding of selective COX-2 inhibitors, as thoroughly explored in the development of COX-2-selective inhibitors. Nonetheless, the steric requirement by the enzyme for the inhibitor is also critical. In the benzo-1,3-dioxolane system, the spacer group combined with 4-substitution on the aryl ring presumably exceeded the steric requirement for significant COX-2 affinity. We have also observed a similar difference in COX-2 potency for 4-fluoro-substituted compounds **22a** and **22d**. In contrast, compounds substituted at the meta-positions were potent COX-2 inhibitors. Among the meta-substituents, compounds substituted with electron-withdrawing groups such as **21e**, **21h**, and **21i** were moderately potent, whereas an electron-donating substituent, as in **21f**, decreased the COX-2 inhibitory potency. COX-2 inhibitory potency and selectivity are extremely sensitive to minor changes in chemical structure within the same chemical series. In this series, 3-fluoro substitution on the aryl ring as in **21c** resulted in a potent COX-2 inhibitor, whereas fluorine substitution at the 2-position decreased the COX-2 potency.

SAR of Aryl Analogues with Substituted Spacers. We found significant differences in COX-2 inhibitor potencies when the spacer group was substituted. Hydroxyl substitution as in **20a** resulted in the loss of COX-2 inhibitory potency (0% inhibition at 10 μM concentration in recombinant enzyme assay), but carbonyl

substitution in the spacer (e.g., compound **22a**) retained the COX-2 inhibitory potency (Table 1). It is noteworthy that compounds **22a** and **22e**, with a carbonyl spacer, exhibited significantly less (10%) COX-2 inhibition at 1 μM concentration in the enzyme assay, whereas the inhibition observed for the same concentration (1 μM) in HWB was considerably higher (25% and 40%, respectively). The carbonyl spacer can increase the polarity of the molecule and/or may have some effect on the hydrophobicity of the compounds. The theoretical *C*log *P* values for the compounds with carbonyl spacer are approximately 1 unit less than the corresponding compounds with methylene spacer (*C* log *P* values: **21a**, 4.41; **22a**, 3.53; **21e**, 4.96; **22e**, 4.09). The 3-aryl-substituted compounds **22c**, **22e**, and **22h** with carbonyl spacer exhibited good COX-2 inhibition (40−50%) at 1 μM concentration in HWB and modest COX-1 inhibition (50−65%) at a very high (100 μM) concentration. In contrast, 4-aryl-substituted compounds **22d** and **22j** did not exhibit any significant COX-2 inhibition (5−10%), even at a high 10 μM concentration in HWB. The COX inhibition by compounds with a carbonyl spacer, **22a−j**, is given in Table 1.

SAR of Methyl Sulfone COX-2 Pharmacophore. Replacement of the methyl sulfone group by a sulfonamide moiety usually decreases COX-2 selectivity but enhances oral bioavailability.[32,54] For the SAR study of this pharmacophore in the bicyclic system, we screened only one sulfonamide (**47**, Scheme 12) analogue of methyl sulfone **21a**. Its COX-2 and COX-1 inhibitory potencies were first determined in the enzyme assay and then in the HWB assay. Sulfonamide substitution, as in **47**, increased the COX-2 inhibitory potency in the enzyme assay. In this series, both the methyl sulfone **21a** and the sulfonamide **47** exhibited excellent COX-2 inhibition in the enzyme assay (Table 3). Sulfonamide **47** was found to be even more potent in the enzyme assay than the corresponding methyl sulfone **21a** with an IC_{50} of 0.05 μM against COX-2 and an IC_{50} of 25 μM against COX-1 (a 500-fold COX-2 selectivity). In the HWB assay, in contrast to methyl sulfone **21a**, the sulfonamide group in **47** abrogated the COX-2 inhibitory activity completely, yet **47** exhibited weak COX-1 inhibitory activity. To confirm this unexpected finding, we repeated the experiment using a known reference sample as a control and obtained the same results. Methyl sulfone and sulfonamide are the two well-known pharmacophores used in the development of COX-2 inhibitors. Even before the HWB assay was developed for the evaluation of COX-2 inhibitors, based on the potency in the enzyme assay, it has been reported and subsequently always presumed that sulfonamide in general increases the oral bioavailability and decreases COX-2 selectivity, which does not seem to be the general case. The sulfonamide **47** did not inhibit COX-2 even at high concentration (100 μM) in HWB, yet inhibited the COX-1 at higher concentrations. We even attempted to determine its IC_{50s} for COX-2 and COX-1 in HWB. For concentrations up to 100 μM, no COX-2 inhibition was observed. The COX-1 IC_{50} for sulfonamide **47** in HWB was 60 μM (Table 4). This divergence in results depending upon assay conditions underscores the importance of screening the compounds in an assay that more accurately reflects the physiological conditions. These data also show that interchangeability of the methyl sulfone group and the sulfonamide group for COX-2 inhibition is dependent upon other structural components, including the central ring system present within a particular inhibitor.

We also studied the effect of fluorine substitution on the methyl sulfone moiety. In this benzo-1,3-dioxolane bicyclic series, when the methyl sulfone was changed to a (fluoromethyl)sulfone as in compound **50**, an approximately 10-fold decrease of COX-2 inhibitory potency was observed in the enzyme assay.

SAR of Pyridyl Analogues. The pyridyl moiety imparts more hydrophilicity to a molecule. It can form a salt in the acidic pH of the GI tract, increasing aqueous solubility and helping to improve the absorption and bioavailability of a molecule, giving rise to enhanced in vivo potency.[55] We evaluated substituted 2- and 3-(pyridylmethyl) analogues for their COX-2 and COX-1 inhibition in the HWB assay. In this series, only the 3-(pyridylmethyl) analogue **27** (Table 2) was active in the enzyme assay: 65% COX-2 inhibition at 10 μM test concentration. The COX-2 inhibitory potency observed for **27** in the enzyme assay was much higher than that observed in the HWB assay. In the HWB assay, **27** showed only 15% COX-2 inhibition at a concentration of 10 μM. The 3-(pyridylmethyl) analogue **28** with a carbonyl spacer was also found to be inactive. The substituted 3-(pyridylmethyl) analogue **35** and the 2-(pyridylmethyl) analogue **31** were not COX-2 inhibitors.

SAR of Nitrogen-Containing Analogues. Since earlier SAR studies demonstrated that cyclohexyl substitution (as in **8a**) resulted in a potent and selective COX-2 inhibitor, another variation was introduced with the aim of retaining COX-2 potency and improving bioavailability. The cyclohexyl ring in **8a** was replaced by piperidine, as in **38a** (Table 2). Introduction of the amine nitrogen into **38a** was detrimental to COX-2 potency. While cyclohexyl analogue **8a** (Table 1) showed 100% COX-2 inhibition at 1 μM in the enzyme assay, its N-containing analogue **38a** was inactive. Substituted analogues **38b−f** exhibited low COX-2 potency in the recombinant enzyme assay; 25−40% inhibitions at 10 μM were observed. The loss in COX-2 inhibitory potency of **38a−f** was postulated to reflect the basicity of the nitrogen. If COX-2 inhibitory potency were compromised to be due to basicity of nitrogen in **38a−f**, then addition of a carbonyl into either the six-member ring as in **42** or into the spacer as in **45b** to give the corresponding amides should be beneficial for COX-2 inhibition. This modification was also guided by the good COX-2 inhibitory potency of **12a** and **22a**, which contain a carbonyl spacer (**12a**: 40% inhibition at 1 μM and 90% inhibition at 10 μM in HWB assay). Unlike compound **12a**, the nitrogen-containing analogue **45b** was a weak COX-2 inhibitor. Interestingly, the lactam **42** showed reasonably potent COX-2 inhibition in the enzymatic assay. However, once again this inhibition profile was not reproduced in the HWB assay (Table 2).

SAR of Spacer and 1,3-Dioxolane Ring. To determine the contribution of the spacer and the dioxolane ring, compounds **65** with no spacer (Scheme 16) and **56**, **59a**, and **60a** with no dioxolane ring (Scheme 15) were screened in the HWB assay, and their potencies were

compared to the corresponding compounds containing those groups. Compounds **21h** and **22h** with methylene and carbonyl spacer groups, respectively, showed excellent COX-2 inhibition in HWB. In contrast, compound **65**, without a spacer group, did not show any COX-2 inhibition at a 10 μM concentration in the HWB assay. Similarly, we also found that the 1,3-dioxolane ring contributed to COX-2 inhibitory potency. Compounds with no dioxolane rings, such as **56**, **59a**, and **60a**, were less potent than the corresponding compounds **7a**, **21c**, and **22c**. Compound **60a** showed weak COX-2 inhibition at a 1 μM concentration in the HWB assay compared to **22c**, which showed 50% inhibition at a 1 μM concentration in WHB. When dimethoxy groups, as in **72**, replaced the 1,3-dioxolane ring in **21h**, the COX-2 inhibitory potency was considerably decreased. Replacement of the 1,3-dioxolane ring in **22c** by 1,4-dioxinyl ring as in **74** also reduced COX-2 inhibitory potency considerably.

In Vivo Activity. To assess the oral activity of benzo-1,3-dioxolane COX-2 inhibitors, selected methyl sulfones **7c** and **21c** were evaluated in an acute inflammation model (the air pouch assay) and were found to be inactive (0% inhibition at 16 mg/kg). The reason for the lack of oral in vivo activity for **7c** and **21c** may reflect limited oral bioavailability. For the purpose of quick evaluation, we decided to directly administer the compound into the air pouch and determine the activity. The potent 3-fluorophenyl-substituted analogue **22c** inhibited 80% of the PGE_2 production in the air pouch (80% inhibition at 2 mg/kg) when administered directly into the air pouch.

Conclusions

We have designed and synthesized a series of novel disubstituted metharyl benzo-1,3-dioxolane compounds, many of which are highly potent and selective COX-2 inhibitors. Our SAR studies demonstrate for the first time that incorporation of a one-carbon spacer group between the central benzo-1,3-dioxolane ring and the cycloalkyl or aryl substituent provides more flexibility and leads to more potent COX-2 inhibitors. In this series, fluorine substitution at meta-position(s) of a phenyl ring, e.g., **21c**, **22c**, and **22h** generated potent and selective COX-2 inhibitors.

Experimental Section

General Comments. Reagents and solvents were generally used as obtained from commercial suppliers. Dry tetrahydrofuran (THF), ethyl ether, hexanes, dichloromethane, dimethylformamide (DMF), and methylsulfoxide (DMSO) were obtained from VWR or Fisher Scientific. Reactions were routinely performed under a nitrogen atmosphere in oven-dried glassware. Melting points were determined with an electrothermal heating block and are uncorrected. ^1H and ^{13}C NMR spectra were determined at 300 and 75.45 MHz, respectively. NMR spectra were recorded in $CDCl_3$ unless otherwise indicated, and chemical shifts are reported relative to tetramethylsilane (δ = 0.00). Routine mass spectra were obtained on a PE SCIEX, API 150 EX instrument with Turbo ion spray injector coupled with a Perkin-Elmer autosampler HPLC unit and 785A UV/vis detector, using an atmospheric pressure ionization method. Elemental microanalyses were performed by Robertson Microlit Laboratories (Madison, NJ). Flash column chromatography was performed using Merck silica gel 60 (270−400 mesh). TLC was performed on a 250 μm precoated Merck silica gel 60 F254 glass-backed plates. Spots were visualized under 254 nm UV light or by staining with phosphomolybdate (10% solution in ethanol) spray reagent.

Assay for Inhibition of Recombinant COX-1 (Human or Ovine) and COX-2 (Human) Enzyme Activity. Inhibition of recombinant human or ovine COX-1 and human COX-2 enzyme activities was measured using either the COX (human) inhibitor screening assay or the COX (ovine) inhibitor screening assay (Cayman Chemical, Ann Arbor, MI, cat. no. 560121 or 560101, respectively), which also contained the prostaglandin screening EIA used for quantification of the prostaglandin product. These commercial assays supplied the COX enzymes. The instructions provided with the assay were followed with some modification. Glass test tubes placed in a 25 °C water bath received 950 μL of reaction buffer (0.1 M Tris-HCl, pH 8.0, containing 5 mM EDTA and 2 mM phenol), 10 μL of a 100 μM heme solution, and 10 μL (5 units) of either human or ovine COX-1 or human COX-2 enzyme, and the resulting mixture was incubated for 2 min. Twenty microliters of test compound or solvent (e.g., DMSO) was added. Each tube was mixed vigorously immediately after this addition. The enzyme was incubated with the inhibitor for 20 min at 25 °C. The enzymatic reaction was then initiated by the addition of 10 μL of freshly prepared 10 mM arachidonic acid (neutralized with KOH) and mixing. After 2 min at 37 °C, the reaction was terminated by addition of 50 μL of 1 M HCl, mixing, and cooling to room temperature. One hundred microliters of a saturated stannous chloride solution (50 mg/mL of 0.1 M HCl) was added and the reaction mixture was allowed to stand at room temperature for at least 5 min. PGs produced in the COX-mediated reactions were quantified by EIA. Activity is expressed as percent inhibition relative to the control reaction containing solvent only (i.e., without test compound).

Assay for Inhibition of COX-1 and COX-2 Enzyme Activity in Human Whole Blood. The assay for COX-1 and COX-2 enzyme activity in human whole blood was performed essentially as described by Young et al.[56] Briefly, human blood from nonfasted, male or female donors who had not taken any aspirin or NSAIDs for 14 days was collected in sodium heparin (20 units per mL blood) and distributed in 1 mL aliquots per well of a 24-well tissue culture plate. The plate was placed on a gently rotating platform shaker in a 5% CO_2 incubator at 37° C for 15 min. Test compounds were dissolved and diluted in DMSO and 1 μL of each dilution of the test compound was added per well in duplicate wells.

To induce COX-2, lipopolysaccharide (LPS) from *Escherichia coli* (LPS, serotype 026:B6 or serotype 0127:B8, Sigma Chemical Co., St. Louis, MO, cat. no. L3755 or L3129, respectively) was added at 10 μg/mL (2 μL of 5 mg/mL LPS in DMSO) to appropriate wells 15 min after the addition of the test compounds. For the stimulation of COX-1, the calcium ionophore A23187 (Sigma Chemical Co., St. Louis, MO, cat. no. C7522) was added to a final concentration of 25 μM (1 μL of 25 mM stock in DMSO) to separate wells 4.5 h after the addition of the test compounds. (All control wells not receiving test compounds, LPS, or A23187 received equal volumes of DMSO) At 30 min after A23187 addition or 5 h after LPS addition, all incubations were terminated by cooling on ice and adding EGTA to a final concentration of 2 mM. The blood samples were then transferred by polyethylene transfer pipets to 15 mL polypropylene centrifuge tubes and centrifuged at 1200g for 10 min at 4 °C. One hundred microliters of plasma was removed from each blood sample and added to 1 mL of methanol in a 15 mL polypropylene centrifuge tube, mixed vigorously, and stored overnight at −20 °C. The next day, the samples were centrifuged at 2000g for 10 min at 4 °C, and the supernatants were transferred to glass tubes and evaporated to dryness. After reconstitution with EIA buffer and appropriate dilution (2000-fold for COX-1 and 500-fold for COX-2), the samples were assayed for TXB_2 using EIA kits supplied by Cayman Chemical Co. (Ann Arbor, MI, cat. no. 519031) in duplicate wells.

Air Pouch Model of Inflammation.[57] Male SD rats (175−200 g, Charles River Laboratories) were used, and the rats were fasted with free access to water at 24 h prior to

experiment. On day zero, animals received subcutaneous injections of 20 mL of sterile air into the intrascapular area of the back. An additional 10 mL of air was injected into the pouch on day −3 to keep the pouch open, allowing the interior membrane to be developed. On day six, vehicle or the test compound in 0.5% methyl cellulose was administered by oral gavage. One hour later inflammation was induced by injecting 1 mL of 1% carrageenan into the air pouch. Three hours after carrageenan injection, rats were sacrificed. Pouch exudates were collected, washed, and the number of leukocytes in the exudate were determined by cell counting with a Coulter counter. The total white blood cells (WBC) counts and percent inhibition of the cell infiltration were calculated. The exudate samples were also assayed for PGE_2 by specific ELISAs (Cayman Chemical Co.).

For determining the activity of COX-2 inhibitor in the air pouch directly, on day six, vehicle or the test compounds in 0.5% methylcellulose were administered by an injection into the air pouch, 1 h prior to the carrageenan injection.

6-Bromo-2*H*-benzo[d]1,3-dioxolene-5-carbaldehyde-(methylsulfonyl)benzene (2). The title compound was synthesized as described.[50] Treatment of piperonal **1** (60 g) with bromine (60 mL) in acetic acid (750 mL) and carbon disulfide (75 mL) containing a catalytic amount of iodine at room temperature, overnight, gave the title compound (69 g, 70% yield): mp 128−130 °C; ^{1}H NMR ($CDCl_3$) δ 10.17 (s, 1H, 7.33 (s, 1H), 7.03 (s, 1H), 6.06 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 190.3, 153.3, 148.1, 128.0, 121.5, 113.2, 108.1, 102.7; LRMS (APIMS) *m/z* 229 (Br 79) and 231 (Br 81) $(M + H)^+$ LRMS (APIMS) *m/z* 229 $(M + H)^+$ and 231 $((M + H) + 2)^+$.

General Procedures. Suzuki Coupling Reaction: Method A. The bromo compound (50 mmol) and 4-(methylthio)benzeneboronic acid **3** (8.4 g, 50 mmol) were dissolved in toluene (500 mL), and sodium carbonate (2 M, 50 mL, 100 mmol) was added. To this reaction mixture was added ethanol (20 mL) followed by tetrakis(triphenylphosphine)-palladium (3.4 g, 2.5 mmol). The reaction mixture was refluxed overnight under a nitrogen atmosphere and then diluted with water (250 mL), the organic layer was separated, and the aqueous layer was extracted with EtOAc (2 × 150 mL). The combined organic extracts were washed with water (4 × 250 mL) and brine (1 × 250 mL), dried over sodium sulfate, and filtered. The filtrate was evaporated under reduced pressure to give the crude product. The product was either purified by trituration with ethyl acetate/hexane or by chromatography on silica gel and elution with hexanes:EtOAc (19:1) to give the title compound as a white solid.

Wittig Reaction: Method B. A suspension of cycloalkyl-(triphenyl)phosphonium bromide (20 mmol) in anhydrous THF (125 mL) was stirred at −78 °C. *n*-BuLi (7 mL of 2.5 M in hexane, 17.5 mmol) was added dropwise to the stirred suspension under nitrogen atmosphere. The reaction mixture was stirred at −78 to −60 °C for over a period of 1 h. The suspension of ylide was then cooled to −78 °C, and the aldehyde (5 mmol) in THF (25 mL) was added dropwise to the ylide solution. The reaction mixture was gently stirred for 1.5 h at −78 °C, slowly allowed to warm to room temperature, and stirred at room temperature overnight. The reaction mixture was then quenched with saturated aqueous ammonium chloride and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with water (1 × 50 mL) and brine (1 × 50 mL), dried over sodium sulfate, and filtered. The filtrate was evaporated and the residue was purified by chromatography on silica gel and elution with hexanes:EtOAc (9:1). This gave the desired product as a white powder in yields varying from 57% to 75%.

Oxone Oxidation Reaction: Method C. The thiomethyl compound (4 mmol) was dissolved in methanol (60 mL) with stirring at room temperature. A solution of Oxone (8 mmol) in water (20 mL) was added. The reaction mixture was stirred at room temperature for 2 h. The solvent methanol was evaporated at reduced pressure and the remainder was diluted with water (25 mL), neutralized with ammonium hydroxide, and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with water (2 × 50 mL) and brine (1 × 25 mL), dried over sodium sulfate, and filtered. The filtrate was evaporated under reduced pressure, and the product was either purified by trituration with ethyl acetate/hexane or by chromatography on silica gel and elution with hexanes:EtOAc (19:1) to give the desired (methylsulfonyl) compound as a white solid in excellent yield.

Grignard Reaction: Method D. The desired Grignard reagent (4 mmol), if not commercially available, was freshly prepared by refluxing the equimolar amounts of haloarene and magnesium in the presence of a catalytic amount of iodine in THF (20 mL). The solution of the corresponding magnesium bromide (4 mmol) in THF (20 mL) was then added to a precooled (0 °C) solution of carbaldehyde (4 mmol) in anhydrous THF (40 mL) under nitrogen atmosphere. The reaction mixture was stirred at 0 °C for 10 min and then at room temperature for 2 h. It was quenched with saturated aqueous ammonium chloride, acidified with 1 N HCl, and then extracted with ethyl acetate (2 × 50 mL). The combined organic extracts were washed with water (1 × 25 mL) and brine (1 × 25 mL), dried over sodium sulfate, and filtered, and the filtrate was evaporated under reduced pressure to give the crude product. Purification by silica gel column chromatography using 20% ethyl acetate in hexane gave the desired compound as a white solid.

Hydrogenation Reaction: Method E. The product to be hydrogenated (1 mmol) was dissolved in a mixture of EtOAc (5 mL) and EtOH (25 mL). The catalyst, 10% palladium on carbon (250 mg), was added under a stream of nitrogen. The hydrogenation was performed at 20 psi of hydrogen for 3 h. The solution was filtered to remove the catalyst, and the filtrate was evaporated under reduced pressure to give the crude product that was triturated with hexanes:EtOAc (5:1) to give the title compound in good yield.

Deoxygenation Reaction Using $NaBH_4$/TFA: Method F. The hydroxyl compound (8 mmol) was dissolved in a minimal amount of CH_2Cl_2 and under argon atmosphere was added to trifluoroacetic acid at 0 °C. The reaction mixture was stirred at 0 °C for 15 min. To the resulting solution was then added, in small portions, sodium borohydride (1.39 g, 36.72 mmol). The reaction mixture was stirred at 0 °C for an additional 30 min. The solvent and trifluoroacetic acid were evaporated under reduced pressure to give a gray foam. Ice-cold water (20 mL) was added to the foam, and the aqueous layer was made basic (pH 8−9) by addition of NaOH (50%). The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic layers were dried over sodium sulfate and filtered. The filtrate was evaporated under reduced pressure to give the crude product that was either purified by recrystallization from CH_2Cl_2:hexanes or by silica gel column chromatography using 20% ethyl acetate in hexane to give the desired compound as a white solid.

PCC Oxidation Reaction: Method G. A suspension of the hydroxyl compound (1 mmol) and alumina (2 g) in anhydrous CH_2Cl_2 (50 mL) was stirred at room temperature. While stirring, pyridinium chlorochromate (3 mmol) was added, and the reaction mixture was stirred at room temperature for 1 h. The mixture was diluted with CH_2Cl_2, and the alumina was removed by filtration. The filtrate was washed with water (1 × 50 mL), saturated aqueous sodium bicarbonate (2 × 50 mL), and brine (1 × 50 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was evaporated under reduced pressure. Purification by flash column chromatography on silica gel and elution with hexanes:EtOAc (19:1) gave the desired compound as a white solid.

N-Alkylation Reaction: Method H. The appropriately substituted halo compound (1.2 mmol) and substituted piperidinyl compound (138 mg, 1.2 mmol) were dissolved in anhydrous DMF (5 mL). Potassium carbonate (830 mg, 6 mmol) was added, and reaction mixture was stirred at room temperature overnight. The reaction mixture was then treated with ice-cold water and extracted with ethyl acetate (2 × 75 mL). The combined organic extracts were washed with water (1 × 50 mL) and brine (1 × 50 mL), dried over sodium sulfate,

and filtered. The filtrate was evaporated under reduced pressure to give the crude product that was purified by flash column chromatography using methanol:dichloromethane (5:95) to give the desired compound as a white solid in high yield.

$NaBH_4$ Reduction: Method I. The carbaldehyde (4 mmol) was dissolved in ethanol (50 mL), and to this solution was added sodium borohydride (12 mmol). The reaction mixture was stirred at room temperature for 2 h. The solvent was evaporated under reduced pressure and the residue was treated with water (25 mL), neutralized with 1 N HCl, and extracted with ethyl acetate (2 × 50 mL). The combined organic extracts were washed with water and brine, dried over sodium sulfate, and filtered. The filtrate was evaporated under reduced pressure to give the crude product. Trituration with 10% ethyl acetate in hexane gave the pure desired compound as a white solid.

6-(4-Methylthiophenyl)-2*H*-benzo[d]1,3-dioxolane-5-carbaldehyde (4). This compound was prepared using method A. It was obtained as a white solid in 88% yield: mp 111−112 °C; ^{1}H NMR ($CDCl_3$) δ 9.74 (s, 1H), 7.41 (s, 1H), 7.29 (m, 4H), 6.80 (s, 1H), 6.07 (s, 2H), 2.52 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 190.3, 152.3, 148.5, 143.3, 140.8, 140.2, 130.9, 128.8, 127.4, 110.1, 106.7; 102.4, 44.4; LRMS (APIMS) *m/z* 273 $(M + H)^+$.

1-(6-(Cyclohexylidenemethyl)(2*H*-benzo[3,4-d]1,3-dioxolan-5-yl))-4-methylthiobenzene (6a). Using method B, compound **6a** was obtained as a white powder in 67% yield: mp 83−84 °C; ^{1}H NMR ($CDCl_3$) δ 7.31 (m, 4H), 6.79 (s, 1H), 6.72 (s, 1H), 5.92 (s, 2H), 5.88 (s, 1H), 2.51 (s, 3H), 2.23 (t, J = 5.6 Hz, 2H), 2.11 (m, 2H), 1.45−1.55 (m, 6H).

4-(6-(Cycloheptylidenemethyl)(2*H*-benzo[3,4-d]1,3-dioxolan-5-yl))-1-methylthiobenzene (6b). Using (cycloheptyl)triphenyl phosphine bromide and following method B, the title compound **6b** was obtained as oil in 57% yield: ^{1}H NMR ($CDCl_3$) δ 7.22 (s, 4H), 6.77 (d, J = 3.1 Hz, 2H), 5.94 (s, 3H), 2.48 (s, 3H), 2.40−2.36 (m, 2H), 2.25−2.20 (m, 2H), 1.63−1.32 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 146.2, 146.0, 143.4, 138.2, 136.6, 134.0, 130.4, 130.2, 125.9, 125.4, 109.9, 109.5, 100.9, 37.4, 31.1, 29.9, 28.9, 28.9, 27.0, 15.8.

1-(6-(Cyclohexylidenemethyl)(2*H*-benzo[3,4-d]1,3-dioxolan-5-yl))-4-(methylsulfonyl)benzene (7a). The compound **7a** was prepared from **6a** by using method C in 56% yield. It was obtained as crystalline solid: mp 147−151 °C; ^{1}H NMR ($CDCl_3$) δ 7.89 (d, J = 8.3 Hz, 2H), 7.84 (d, J = 8.3 Hz, 2H), 6.77 (s, 1H), 6.72 (s, 1H), 5.98 (s, 2H), 5.84 (s, 1H), 3.07 (s, 3H), 2.14 (t, J = 5.6 Hz, 2H), 2.08 (m, 2H), 1.51−1.30 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 147.2, 147.1, 146.4, 143.2, 138.3, 135.5, 130.6, 130.5, 126.8, 120.9, 110.5, 109.4, 101.2, 44.5, 36.9, 29.5, 28.2. 27.3, 26.4; LRMS (APIMS) *m/z* 371 $(M + H)^+$. Anal. ($C_{21}H_{22}SO_4$) C, H.

4-(6-(Cycloheptylidenemethyl)(2*H*-benzo[3,4-d]1,3-dioxolan-5-yl))-1-(methylsulfonyl)benzene (7b). The compound **7b** was prepared from **6b** using method C in 75% yield. It was obtained as a white solid: mp 168−169 °C; ^{1}H NMR ($CDCl_3$) δ 7.91 (d, J = 8.3 Hz, 2H), 7.51 (d, J = 8.2 Hz, 2H), 6.79 (d, J = 2.1 Hz, 2H), 6.00 (s, 2H), 5.92 (s, 1H), 3.09 (s, 3H), 2.32 (t, J = 14.4 Hz, 2H), 2.23−2.17 (m, 2H), 1.61−1.51 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 147.3, 146.4, 145.0, 138.4, 132.5, 131.0, 130.7, 126.8, 124.5, 110.3, 109.5, 101.3, 44.6, 37.5, 31.2, 29.9, 29.0, 28.9, 26.9; LRMS (APIMS) *m/z* 402 $(M + NH_4)^+$. Anal. ($C_{22}H_{24}SO_4$) C, H.

4-(6-(Cyclopentylidenemethyl)(2*H*-benzo[3,4-d]1,3-dioxolan-5-yl))-1-(methylsulfonyl)benzene (7c). A suspension of cyclopentyltriphenylphosphine bromide **5c** (1.24 g, 3 mmol) in anhydrous THF (15 mL) was stirred at 0 °C under nitrogen atmosphere. A solution of *t*-BuOK (2.5 mL of 1M in THF, 2.5 mmol) was added dropwise and stirred for 15 min. To the resulting dark orange colored mixture was added the carbaldehyde **15** (3.04 g, 3 mmol) in anhydrous THF (10 mL) and DMF (10 μL) dropwise. The reaction mixture was stirred at 0 °C for 30 min and then slowly allowed to warm to room temperature and stirred for 3 h at room temperature. The reaction was quenched with saturated aqueous ammonium chloride, and the organic layer was separated. The aqueous layer was diluted and extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. Purification by flash column chromatography using 20% ethyl acetate in hexanes as the eluant gave the title compound **7c** as a white solid (280 mg, 72% yield): mp 145−147 °C; ^{1}H NMR ($CDCl_3$) δ 7.94−7.91 (m, 2H), 7.51−7.48 (m, 2H), 6.97 (s, 1H), 6.75 (s, 1H), 6.00−5.97 (m, 3H), 3.11 (s, 3H), 2.41 (t, J = 6.8 Hz, 2H), 2.31 (t, J = 7.0 Hz, 2H), 1.77−1.54 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 147.4, 147.3, 146.9, 146.0, 138.5, 132.3, 131.1, 130.7, 126.9, 111.0, 109.6, 108.8, 101.2, 44.5, 34.8, 30.9, 26.8, 25.4; LRMS (APIMS) *m/z* 374 $(M + NH_4)^+$. Anal. ($C_{20}H_{20}SO_4$) C, H.

1-(6-(Cyclohexylmethyl)(2*H*-benzo[3,4-d]1,3-dioxolen-5-yl))-4-(methylsulfonyl)benzene (8a). The product **7a** was converted to **8a** using method E to give the title compound **8a** in 54% yield: mp 112−116 °C; ^{1}H NMR ($CDCl_3$) δ 7.94 (d, J = 8.2 Hz, 2H), 7.43 (d, J = 8.2 Hz, 2H), 6.75 (s, 1H), 6.61 (s, 1H), 5.97 (s, 2H), 3.10 (s, 3H), 2.34 (d, J = 5.1 Hz, 2H), 1.6−0.80 (m, 11H); ^{13}C NMR ($CDCl_3$) δ 148.1, 147.4, 145.5, 138.7, 133.3, 132.5, 130.7, 127.1, 109.8, 109.5, 101.1, 44.5, 40.2, 39.8, 32.9 (2 × C), 26.3, 26.2 (2 × C); LRMS (APIMS) *m/z* 390 $(M + NH_4)$. Anal. ($C_{21}H_{24}SO_4$) C, H.

4-(6-(Cycloheptylsmethyl)(2*H*-benzo[3,4-d]1,3-dioxolan-5-yl))-1-(methylsulfonyl)benzene (8b). As described above, the product **8a** was similarly converted to **8b** using method E to give the title compound **8b** in 80% yield: mp 89−92 °C; ^{1}H NMR ($CDCl_3$) δ 7.91 (d, J = 8.3 Hz, 2H), 7.39 (d, J = 8.3 Hz, 2H), 6.72 (s, 1H), 6.57 (s, 1H), 5.92 (s, 2H), 3.07 (s, 3H), 2.33 (d, J = 7.1 Hz, 2H), 1.53−1.14 (m, 11H), 0.90 (q, J = 10.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 147.9, 147.4, 145.4, 138.6, 133.3, 132.8, 130.6, 127.0, 109.6, 109.4, 101.0, 44.4, 41.1, 40.4, 33.9, 28.1, 26.0; LRMS (APIMS) *m/z* 404 $(M + NH_4)^+$. Anal. ($C_{22}H_{26}SO_4$) C, H.

4-(6-(Cyclopenthylmethyl)(2*H*-benzo[3,4-d]1,3-dioxolan-5-yl))-1-(methylsulfonyl)benzene (8c). Compound **8c** was prepared by method E. The pure compound was obtained a white solid, in 83% yield: mp 103−105 °C; ^{1}H NMR ($CDCl_3$) δ 7.98−7.94 (m, 2H), 7.48−7.44 (m, 2H), 6.80 (s, 1H), 6.64−6.61 (m, 1H), 5.98 (s, 2H), 3.10 (s, 3H), 2.49−2.43 (m, 2H), 1.98−1.83 (m, 1H), 1.59−1.40 (m, 6H), 0.98−0.78 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 148.0, 147.5, 145.5, 138.7, 133.5, 133.0, 130.7, 127.1, 109.7, 109.6, 101.1, 44.6, 41.9, 38.3, 32.3, 24.6; LRMS (APIMS) *m/z* 376 $(M + NH_4)^+$. Anal. ($C_{20}H_{22}SO_4$) C, H.

Cyclohexyl(6-(4-methylthiophenyl)(2*H*-benzo[d]1,3-dioxolan-5-yl))methan-1-ol (10a). The compound **10a** was prepared by using method D. The product was obtained as a white solid in 93% yield: mp 110−112 °C; ^{1}H NMR ($CDCl_3$) δ 7.26 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 7.01 (s, 1H), 6.64 (s, 1H), 5.97 (dd, J = 4.1 and 1.3 Hz, 2H), 4.4 (dd, J = 8.7 and 3.2 Hz, 1H), 2.52 (s, 3H), 2.0 (m, 1H, OH), 1.80−1.50 (m, 5H), 1.20−0.5 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 147.3, 146.4, 137.9, 137.0, 135.0, 134.8, 130.0 (2 × C), 126.2 (2 × C), 109.7, 106.2, 101.1, 74.9, 44.9, 29.3, 29.2, 26.2, 26.0, 28.9, 15.7; LRMS (APIMS) *m/z* 730 $(2\ M + NH_4)^+$, 339 $(M - OH)^+$.

1-(6-(Cyclohexylhydroxymethyl)(2*H*-benzo[3,4-d]1,3-dioxolan-5-yl))-4-(methylsulfonyl)benzene (11a). The thiomethyl compound **10a** was converted to **11a** using method C. The product **11a** was obtained in 92% yield: mp 140−142 °C; ^{1}H NMR ($CDCl_3$) δ 7.93 (d, J = 8.3 Hz, 2H), 7.46 (d, J = 8.4 Hz, 2H), 7.03 (s, 1H), 6.60 (s, 1H), 5.98 (s, 2H), 4.21 (d, J = 6.8 Hz, 1H), 3.1 (s, 3H), 2.85 (br s, 1H, OH), 2.0 (m, 1H), 1.7−0.5 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 148.1, 147.1, 146.7, 139.0, 134.8, 133.4, 130.7 (2 × C), 127.3 (2 × C), 109.2, 106.6, 101.4, 74.8, 45.0, 44.5, 29.3, 29.1, 26.1, 25.9, 25.8; LRMS (APIMS) *m/z* 406 $(M + NH_4)^+$.

Cyclohexyl 6-(4-(Methylsulfonyl)phenyl)(2*H*-benzo-[d]1,3-dioxolan-5-yl) Ketone (12a). Oxidation of **11a** using method G gave **12a** in 82% yield: mp 172−174 °C; ^{1}H NMR ($CDCl_3$) δ 7.93 (d, J = 8.3 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 7.03 (s, 1H), 6.80 (s, 1H), 6.05 (s, 2H), 3.06 (s, 3H), 2.25 (m, 1H), 1.7−1.5 (m, 5H), 1.30−0.80 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 149.4, 147.7, 139.3, 134.0, 133.8, 129.6 (2 × C), 127.4 (2 × C), 110.2, 108.6, 102.0, 49.7, 44.5 (2 × C), 29.1 (2 × C), 25.6 (2 ×

C); LRMS (APIMS) *m/z* 404 (M + NH_4), 387 (M + H)$^+$. Anal. ($C_{21}H_{22}SO_5$) C, H.

(6-(4-Methylthiophenyl)-2*H*-benzo[d]1,3-dioxolen-5-yl-)methan-1-ol (13). The carbaldehyde **4** was reduced to **13** by method I. The title compound **13** was obtained as a white solid in 66% yield: mp 95−97 °C; ^{1}H NMR ($CDCl_3$) δ 7.25 (m, 4H), 6.99 (s, 1H), 6.72 (s, 1H), 5.96 (s, 2H), 4.41 (s, 2H), 2.50 (s, 3H), 1.95 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 147.0, 146.8, 137.3, 137.1, 134.6, 131.7, 129.6 (2 × C), 126.2 (2 × C), 109.9, 108.7, 101.1, 62.7, 15.7; LRMS (APIMS) *m/z* 292 (M + NH_4)$^+$.

1-(6-(Hydroxymethyl)(2*H*-benzo[3,4-d]1,3-dioxolen-5-yl)-4-(methylsulfonyl)benzene (14). The compound **13** was converted to **14** by method **C**. The pure product **14** was obtained as a white crystalline solid, in 97% yield: mp 163 °C; ^{1}H NMR ($CDCl_3$) δ 7.95 (d, J = 8.1 Hz, 2H), 7.55 (d, J = 8.2 Hz, 2H), 7.03 (s, 1H), 6.72 (s, 1H), 6.00 (s, 2H), 4.43 (s, 2H), 3.09 (s, 3H), 2.1 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 147.9, 147.3, 146.3, 139.1, 133.3, 131.8, 130.3, 127.3, 109.7, 109.3, 101.4, 62.6, 44.5; LRMS (APIMS) *m/z* 324 (M + NH_4)$^+$.

6-(4-(Methylsulfonyl)phenyl)-2*H*-benzo[d]1,3-dioxolane-5-carbaldehyde (15). Compound **14** was oxidized using method G to give the title compound as a white solid, in 68% yield: mp 152−153 °C; ^{1}H NMR ($CDCl_3$) δ 9.74 (s, 1H), 8.06 (d, J = 8.2 Hz, 2H), 7.59 (d, J = 8.2 Hz, 2H), 7.51 (s, 1H), 6.86 (s, 1H), 6.16 (s, 2H), 3.16 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 189.3, 152.3, 148.5, 143.3, 140.9, 130.9 (2 × C), 128.8, 127.4 (2 × C), 110.0, 106.7, 102.4, 49.7, 44.4; LRMS (APIMS) *m/z* 322 (M + NH_4)$^+$, 305 (M + H)$^+$. Anal. ($C_{14}H_{12}SO_3$) C, H.

1-(6-(Chloromethyl)(2*H*-benzo[3,4-d]1,3-dioxolan-5-yl))-4-(methylsulfonyl)benzene (16). To a solution of methyl sulfone **14** (1.53 g, 5 mmol) in anhydrous benzene (35 mL) was added thionyl chloride (0.8 mL) followed by a catalytic amount of pyridine (3 or 4 drops). The reaction mixture was stirred at room-temperature overnight. The solvent was evaporated under reduced pressure, and the residue on addition of hexane gave a white solid. The product was used without further purification. The sample was characterized after purification by silica gel column chromatography using ethyl acetate hexane (1:1): mp 146−148 °C; ^{1}H NMR ($CDCl_3$) δ 8.00 (d, J = 8.3 Hz, 2H), 7.6 (d, J = 8.3 Hz, 2H), 6.99 (s, 1H), 6.71 (s, 1H), 6.02 (s, 2H), 4.38 (s, 2H), 3.11 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 148.1, 145.7, 139.6, 134.1, 130.2, (2 × C), 128.5, 127.4 (2 × C), 110.3, 109.7, 101.7, 44.4; LRMS (APIMS) *m/z* 342 (M + NH_4)$^+$. Anal. ($C_{14}H_{14}SO_3$) C, H.

Using methods D, C, E, G, and I and carbaldehyde **4** as a starting material, compounds **21a−j** and compounds **22a−j** were prepared good yields. Spectral data for the few representative examples are given below.

(6-(4-Methylthiophenyl)(2*H*-benzo[d]1,3-dioxolan-5-yl))phenylmethan-1-ol (19a): white solid; mp 96−99 °C; ^{1}H NMR ($CDCl_3$) δ 7.21 (m, 9H), 6.95 (s, 1H), 6.69 (s, 1H), 5.94 (s, 2H), 5.82 (s, 1H), 2.50 (s, 3H), 2.24 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 147.2, 146.7, 143.9, 137.4, 137.3, 134.9, 134.5, 129.9, 128.2, 127.1, 126.3, 126.2, 109.7, 107.5, 101.1, 72.0, 15.7; LRMS (APIMS) *m/z* 333 (M − OH)$^+$, 718 (2M + NH_4)$^+$.

(2-Fluorophenyl)(6-(4-methylthiophenyl)(2*H*-benzo[d]1,3-dioxolan-5-yl))methan-1-ol (19b): white solid; mp 130−135 °C; ^{1}H NMR ($CDCl_3$) δ 7.51 (t, J = 8.3 Hz, 1H), 7.32 (d, J = 8.4 Hz, 1H), 7.30−7.20 (m, 5H), 6.91 (m, 1H), 6.85 (s, 1H), 6.71 (s, 1H), 6.02 (s, 1H), 5.94 (s, 2H), 2.50 (s, 3H), 2.31 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 161.3, 158.0, 146.8, 137.3, 134.9, 133.4, 130.8, 129.8, 128.8, 127.5, 127.1, 126.2, 123.9, 115.2, 110.0, 107.4, 101.2, 67.0, 15.8; LRMS (APIMS) *m/z* 351 (M − OH)$^+$, 754 (2M + NH_4)$^+$.

(3-Fluorophenyl)(6-(4-methylthiophenyl)(2*H*-benzo[d]1,3-dioxolan-5-yl))methan-1-ol (19c): white solid; mp 97−99 °C; ^{1}H NMR ($CDCl_3$) δ 7.28−7.18 (m, 5H), 6.92 (m, 3H), 6.87 (s, 1H), 6.70 (s, 1H), 5.96 (d, J = 1.8 Hz, 2H), 5.79 (d, J = 3.6 Hz, 1H), 2.51 (s, 3H), 2.18 (d, J = 3.8 Hz, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 164.4, 161.1, 147.4 (d, J = 34 Hz), 146.6 (d, J = 6.6 Hz), 137.7, 137.2, 134.7, 134.4, 129.8 (2 × C), 126.9 (d, J = 8.2 Hz), 126.3 (2 × C), 121.9, 114.0 (d, J = 21 Hz), 113.3 (d, J = 22 Hz), 109.8, 107.4, 101.3, 71.5, 15.7; LRMS (APIMS) *m/z* 386 (M + NH_4)$^+$, 754 (2M + NH_4)$^+$.

(4-Fluorophenyl)(6-(4-methylthiophenyl)(2*H*-benzo[d]1,3-dioxolan-5-yl))methan-1-ol (19d): colorless thick oil; ^{1}H NMR ($CDCl_3$) δ 7.25 (d, J = 8.3 Hz, 2H), 7.15−7.00 (m, 3H), 7.00−6.84 (m, 4H), 6.8 (s, 1H), 5.96 (s, 2H), 5.79 (s, 1H), 2.50 (s, 3H), 2.11 (br s, 1H, OH); LRMS (APIMS) *m/z* 351 (M − OH)$^+$, 754 (2M + NH_4)$^+$.

(3-Methylphenyl)(6-(4-methylthiophenyl)(2*H*-benzo[d]1,3-dioxolan-5-yl))methan-1-ol (19e): colorless thick oil; ^{1}H NMR ($CDCl_3$) δ 7.26−7.12 (m, 5H), 7.02−6.95 (m, 4H) 6.68 (s, 1H), 5.94 (d, J = 1.2 Hz, 2H), 5.77 (d, J = 3.3 Hz, 1H), 2.50 (s, 3H), 2.29 (s, 3H), 2.16−2.13 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 147.3, 146.7, 143.8, 137.8, 137.4, 135.1, 134.6, 130.0, 128.1, 127.9, 127.0, 126.2, 123.4, 109.8, 107.5, 101.2, 72.1, 21.4, 15.8; LRMS (APIMS) *m/z* 746 (2M + NH_4)$^+$, 347 (M − OH)$^+$.

(3-Methoxyphenyl)(6-(4-methylthiophenyl)(2*H*-benzo[d]1,3-dioxolan-5-yl))methan-1-ol (19f): white solid; mp 95 °C; ^{1}H NMR ($CDCl_3$) δ 7.28−7.25 (m, 2H), 7.21 (s, 2H), 6.95 (d, J = 0.5 Hz, 1H), 6.82−6.77 (m, 2H), 6.75 (s, 2H), 6.69 (d, J = 0.9 Hz, 1H), 5.97−5.95 (m, 2H), 5.80 (d, J = 3.8 Hz, 1H), 3.76 (d, J = 0.9 Hz, 3H), 2.51 (d, J = 0.9 Hz, 3H), 2.04−2.01 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 159.6, 147.4, 146.8, 145.6, 137.5, 137.4, 134.9, 134.7, 130.0, 129.3, 126.3, 118.7, 112.6, 112.1, 109.8, 107.5, 101.2, 72.0, 55.2, 15.8; LRMS (APIMS) *m/z* 778 (2M + NH_4)$^+$, 363 (M − OH)$^+$.

(2-Fluoro-5-methylphenyl)(6-(4-methylthiophenyl)(2*H*-benzo[d]1,3-dioxolen-5-yl))methan-1-ol (19g): white solid; mp 110 °C; ^{1}H NMR ($CDCl_3$) δ 7.26−7.18 (m, 5H), 7.01−6.98 (m, 1H), 6.87 (s, 1H), 6.82−6.76 (m, 1H), 6.69 (s, 1H), 5.97 (s, 1H), 5.95 (s, 2H), 2.50 (s, 3H), 2.31 (s, 3H), 2.10 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 147.1, 146.8, 137.4, 137.3, 135.0, 133.4, 133.4, 130.2, 129.8, 129.3, 129.2, 128.0, 127.9, 126.2, 115.0, 114.8, 110.0, 107.5, 101.2, 67.2, 20.8, 15.8; LRMS (APIMS) *m/z* 782 (2M + NH_4)$^+$, 365 (M − OH)$^+$.

1-(6-(Hydroxyphenylmethyl)(2*H*-benzo[3,4-d]1,3-dioxolan-5-yl))-4-(methylsulfonyl)benzene (20a): white solid; mp 144−148 °C; ^{1}H NMR ($CDCl_3$) δ 7.89 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 8.0 Hz, 2H), 7.23 (m, 3H), 7.12 (m, 2H), 7.0 (s, 1H), 6.65 (s, 1H), 5.97 (s, 2H), 5.69 (s, 1H), 3.06 (s, 3H), 2.44 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 148.1, 146.9, 146.5, 143.4, 139.2, 134.9, 133.0, 130.5, 128.3, 127.4, 127.1, 126.3, 109.4, 107.8, 101.4, 72.1, 44.5; LRMS (APIMS) *m/z* 400 (M + NH_4)$^+$.

1-(6-((2-Fluorophenyl)hydroxymethyl)(2*H*-benzo[3,4-d]1,3-dioxolan-5-yl))-4-(methylsulfonyl)benzene (20b): white solid; mp 163−169 °C; ^{1}H NMR ($CDCl_3$) δ 7.85 (d, J = 6.4 Hz, 2H), 7.46 (d, J = 6.5 Hz, 2H), 7.4−7.1 (m, 3H), 6.85 (s, 1H), 6.80 (m, 1H), 6.61 (s, 1H), 5.99 (s, 2H), 5.91 (d, J = 3.8 Hz, 1H), 3.07 (s, 3H), 2.44 (d, J = 4.1 Hz, 1H, OH); LRMS (APIMS) *m/z* 418 (M + NH_4)$^+$. Anal. ($C_{21}H_{17}SFO_5$) C, H.

1-(6-((3-Fluorophenyl)hydroxymethyl)(2*H*-benzo[3,4-d]1,3-dioxolan-5-yl))-4-(methylsulfonyl)benzene (20c): white solid; mp 163−169 °C; ^{1}H NMR ($CDCl_3$) δ 7.92 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H), 7.4 (m, 1H), 6.93 (s, 1H), 6.88 (m, 3H), 6.67 (s, 1H), 5.99 (d, J = 1.8 Hz, 2H), 5.68 (d, J = 3.2 Hz, 1H), 3.08 (s, 3H), 2.50 (d, J = 3.8 Hz, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 164.4, 161.1, 148.2, 147.2, 146.4, 139.4, 134.5, 133.2, 130.5 (2 × C), 129.9 (d, J = 8 Hz), 127.3 (2 × C), 121.9, 114.2 (d, J = 21 Hz), 113.3 (d, J = 22 Hz), 109.5, 107.8, 101.6, 71.5, 44.5; LRMS (APIMS) *m/z* 418 (M + NH_4)$^+$.

1-(6-((4-Fluorophenyl)hydroxymethyl)(2*H*-benzo[3,4-d]1,3-dioxolan-5-yl))-4-(methylsulfonyl)benzene (20d): white solid; mp 85−95 °C; ^{1}H NMR ($CDCl_3$) δ 7.90 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 8.2 Hz, 2H), 6.89 (d, J = 7.1 Hz, 4H), 6.69 (s, 1H), 6.68 (s, 1H), 5.98 (s, 2H), 3.77 (s, 2H), 3.07 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 162.8, 159.6, 147.7, 147.1, 146.8, 139.0, 136.5, 133.3, 131.5 (2 × C), 130.3, 129.8 (2 × C), 129.7, 127.2, 115.0, 110.4, 109.7, 101.3, 44.5, 37.9; LRMS (APIMS) *m/z* 418 (M + NH_4)$^+$.

4-(6-(Hydroxy(3-methylphenyl)methyl)(2*H*-benzo[3,4-d]1,3-dioxolan-5-yl))-1-(methylsulfonyl)benzene (20e): white solid; mp 154 °C; ^{1}H NMR ($CDCl_3$) δ 7.93, (d, J = 8.5 Hz, 2H), 7.46 (d, J = 8.4 Hz, 2H), 7.16 (t, J = 7.6 Hz, 1H), 7.05−7.04 (m, 2H), 6.95−6.90 (m, 2H), 6.68 (s, 1H), 6.01−6.00 (m, 2H), 5.68 (d, J = 3.5 Hz, 1H), 3.09 (s, 3H), 2.29 (s, 3H), 2.04 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 148.0, 147.0, 146.6, 143.4,

139.2, 138.1, 135.0, 133.0, 130.6, 128.3, 128.3, 127.2, 127.0, 123.4, 109.4, 107.8, 101.5, 72.2, 44.5, 21.4; LRMS (APIMS) *m/z* 414 $(M + NH_4)^+$, 379 $(M - OH)^+$.

1-(6-(Hydroxy(3-methoxyphenyl)methyl)(2*H*-benzo-[3,4-d]1,3-dioxolan-5yl))-4-(methylsulfonyl)benzene (20f): white solid (1.00 g, 93% yield); mp 154 °C; ^{1}H NMR ($CDCl_3$) δ 7.92 (d, J = 8.1 Hz, 2H), 7.47 (d, J = 8.0 Hz, 2H), 7.23−7.1 (m, 1H), 7.01 (s, 1H), 6.77−6.67 (m, 4H), 5.99 (d, J = 2.6 Hz, 2H), 5.67 (s, 1H), 3.75 (s, 3H), 3.08 (s, 3H), 2.32 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 159.6, 148.0, 147.0, 146.5, 145.2, 139.2, 134.8, 133.0, 130.6, 129.4, 127.2, 118.7, 112.5, 112.3, 109.4, 107.7, 101.5, 72.0, 55.2, 44.5; LRMS (APIMS) *m/z* 430 $(M + NH_4)^+$.

4-(6-((2-Fluoro-5-methylphenyl)hydroxymethyl)(2*H*-benzo[3,4-d]1,3-dioxolan-5-yl))-1-(methylsulfonyl)benzene (20g): white solid; mp 169−171 °C; ^{1}H NMR ($CDCl_3$) δ 7.92 (d, J = 8.4 Hz, 2H), 7.49 (d, J = 8.4 Hz, 2H), 7.26−7.22 (m, 1H), 7.00−6.98 (m, 1H), 6.94 (s, 1H), 6.80−6.74 (m, 1H), 6.67 (s, 1H), 6.00−5.99 (m, 2H), 5.88 (s, 1H), 3.10 (s, 3H), 2.31 (s, 3H), 2.25 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 147.9, 147.1, 146.4, 139.2, 133.7, 133.3, 130.5, 130.1, 129.6, 129.5, 127.7, 127.2, 115.0, 114.8, 109.6, 107.7, 101.5, 66.8, 44.5, 20.8; LRMS (APIMS) *m/z* 846 $(2M + NH_4)^+$, 432 $(M + NH_4)^+$.

4-(Methylsulfonyl)-1-(6-benzyl(2*H*-benzo[3,4-d]1,3-dioxolan-5-yl))benzene (21a): white solid; mp 111−114 °C; ^{1}H NMR ($CDCl_3$) δ 8.1 (d, J = 8.4 Hz, 2H), 7.90 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 8.3 Hz, 2H), 7.25−7.10 (m, 3H), 6.94 (d, J = 7.0 Hz, 2H), 6.71 (s, 1H), 6.70 (s, 1H), 5.99 (s, 2H), 3.81 (s, 2H), 3.08 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 147.8, 147.3, 146.2, 140.9, 138.9, 133.8, 133.4, 131.7, 130.4, 130.2, 128.52, 128.48, 127.2, 126.1, 110.6, 109.7, 101.3, 44.6, 38.8; LRMS (APIMS) *m/z* 384 $(M + H)^+$. Anal. ($C_{21}H_{18}SO_4$) C, H.

1-(6-((2-Fluorophenyl)methyl)(2*H*-benzo[3,4-d]1,3-dioxolan-5-yl))-4-(methylsulfonyl)benzene (21b): white solid; mp 98−99 °C; ^{1}H NMR ($CDCl_3$) δ 7.92 (d, J = 6.8 Hz, 2H), 7.42 (d, J = 7.6 Hz, 2H), 7.20 (m, 1H), 7.05−6.80 (m, 3H), 6.69 (s, 1H), 6.68 (s, 1H), 5.97 (s, 2H), 3.81 (s, 2H), 3.08 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 162.3, 159.05, 147.7, 147.2, 146.2, 139.0, 133.4, 130.5, 130.3 (2 × C), 127.9, 127.2 (2 × C), 115.3, 115.0, 110.2, 109.7, 101.3, 44.55, 31.8; LRMS (APIMS) *m/z* 402 $(M + NH_4)^+$. Anal. ($C_{21}H_{17}FSO_4$) C, H.

1-(6-((3-Fluorophenyl)methyl)(2*H*-benzo[3,4-d]1,3-dioxolan-5-yl))-4-(methylsulfonyl)benzene (21c): white solid; mp 110−111 °C; ^{1}H NMR ($CDCl_3$) δ 7.89 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.3 Hz, 2H), 7.15 (m, 1H), 6.83 (dt, J = 5.2 and 2.3 Hz, 1H), 6.70 (m, 3H), 6.60 (d, J = 9.9 Hz, 1H), 5.99 (s, 2H), 3.81 (s, 2H), 3.08 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 164.5, 161.2, 147.9, 146.4, 143.5, 139.1, 133.6, 130.9, 130.4 (2 × C), 129.9 (d, J = 8.2 Hz), 127.2 (2 × C), 124.2, 115.3 (d, J = 21.5 Hz), 113.9 (d, J = 21 Hz), 110.6, 109.8, 101.4, 44.5, 38.6; LRMS (APIMS) *m/z* 402 $(M + NH_4)^+$. Anal. ($C_{21}H_{17}SFO_4$) C, H.

1-(6-((4-Fluorophenyl)methyl)(2*H*-benzo[3,4-d]1,3-dioxolan-5-yl))-4-(methylsulfonyl)benzene (21d): white solid; mp 130−132 °C; ^{1}H NMR ($CDCl_3$) δ 7.9 (d, J = 8.4 Hz, 2H), 7.3 (d, J = 8.4 Hz, 2H), 6.9 (d, J = 8.3 Hz, 4H), 6.9 (s, 1H), 6.8 (s, 1H), 5.97 (s, 2H), 3.80 (s, 2H), 3.1 (s, 3H); LRMS (APIMS) *m/z* 402 $(M + NH_4)^+$. Anal. ($C_{21}H_{17}SFO_4$) C, H.

4-{6-[(3-Methylphenyl)methyl](2*H*-benzo[3,4-d]1,3-dioxolan-5-yl)}-1-(methylsulfonyl)benzene (21e): white solid; mp 84−86 °C; ^{1}H NMR ($CDCl_3$) δ 7.91 (d, J = 8.3 Hz, 2H), 7.42 (d, J = 8.3 Hz, 2H), 7.11 (t, J = 7.8 Hz, 1H), 6.98 (d, J = 7.6 Hz, 1H), 6.76−6.71 (m, 4H), 5.99 (s, 2H), 3.78 (s, 2H), 3.09 (s, 3H), 2.27 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 147.7, 147.4, 146.1, 140.8, 138.9, 138.0, 133.4, 131.9, 130.4, 129.3, 128.3, 127.2, 126.8, 125.6, 110.6, 109.6, 101.3, 44.5, 38.7, 21.4; LRMS (APIMS) *m/z* 398 $(M + NH_4)^+$. Anal. ($C_{22}H_{20}SO_4$) C, H.

4-(6-(3-Methoxyphenyl)methyl)(2*H*-benzo[3,4-d]1,3-dioxolan-5-yl))-1-(methylsulfonyl)benzene (21f): white solid; mp 125−126 °C; ^{1}H NMR ($CDCl_3$) δ 7.90 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 7.14 (t, J = 7.9 Hz, 1H), 6.73−6.70 (m, 3H), 6.56−6.53 (m, 1H), 6.47 (s, 1H), 5.98 (s, 2H), 3.79 (s, 2H), 3.73 (s, 3H), 3.08 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 159.6, 147.7, 147.3, 146.2, 142.6, 138.9, 133.4, 131.5, 130.4, 129.3, 127.2, 120.9, 114.7, 111.0, 110.6, 109.7, 101.3, 55.1, 44.5, 38.7; LRMS (APIMS) *m/z* 810 $(2M + NH_4)^+$, 397 $(M + H)^+$. Anal. ($C_{22}H_{20}SO_5$) C, H.

4-{6-[(2-Fluoro-5-methylphenyl)methyl](2*H*-benzo[3,4-d]1,3-dioxolan-5-yl)}-1-(methylsulfonyl)benzene (21g): white solid; mp 98−100 °C; ^{1}H NMR ($CDCl_3$) δ 7.93 (d, J = 8.2 Hz, 2H), 7.43 (d, J = 8.2 Hz, 2H), 7.00−6.90 (m, 1H), 6.82 (t, J = 9.1 Hz, 1H), 6.69 (s, 2H), 6.64 (d, J = 7.2 Hz, 1H), 5.99 (s, 2H), 3.98 (s, 2H), 3.09 (s, 3H), 2.21 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 157.3, 147.8, 147.3, 146.2, 139.0, 133.4, 131.0, 130.7, 130.4, 128.4, 127.2, 115.0, 114.7, 110.2, 109.7, 101.3, 44.6, 31.9, 20.7; LRMS (APIMS) *m/z* 416 $(M + NH_4)^+$.

4-(1-(3′,5′-Difluorophenyl)-1-hydroxymethyl)-1,2-methylenedioxy-5-(4-methylthiophenyl)benzene. (3,5-Difluorophenyl)(6-(4-methylthiophenyl)(2*H*-benzo[d]1,3-dioxolan-5-yl))methan-1-ol (19h). The resulting product was used for the next reaction without further purification.

4-(1-(3′,5′-Difluorophenyl)-1-hydroxymethyl)-1,2-methylenedioxy-5-(4-methylsulfonylphenyl)benzene (20h). The product was used without purification.

5-(1-(3′,5′-Difluorophenyl)methyl)-1,2-methylenedioxy-4-(4-methylsulfonylphenyl)benzene (21h). Compound **21h** was prepared by method F to give a light brown solid in 63% overall yield for three steps from **19h**): mp 140−141°C; ^{1}H NMR ($CDCl_3$) δ 7.91 (m, 2H), 7.36 (m, 2H), 6.71 (s, 1H), 6.70 (s, 1H), 6.59 (m, 1H), 6.42 (m, 2H), 6.02 (s, 2H), 3.80 (s, 2H), 3.09 (s, 3H); LRMS (APIMS) *m/z* 420 $(M + NH_4)^+$.

4-{6-[(3-Chlorophenyl)methyl](2*H*-benzo[3,4-d]1,3-dioxolan-5-yl)}-1-(methylsulfonyl)benzene (21i): white solid; mp 112−113 °C; ^{1}H NMR ($CDCl_3$) δ 7.91 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.3 Hz, 2H), 7.13−7.12 (m, 2H), 6.87 (s, 1H), 6.82−6.80 (m, 1H), 6.70 (s, 2H), 6.00 (s, 2H), 3.79 (s, 2H), 3.09 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 147.8, 147.1, 146.4, 142.9, 139.1, 134.1, 133.6, 130.8, 130.3, 129.6, 128.5, 127.2, 126.7, 126.3, 110.5, 109.8, 101.4, 44.5, 38.5; LRMS (APIMS) *m/z* 418 $(M + NH_4)^+$. Anal. ($C_{21}H_{17}ClO_4$) C, H.

4-{6-[(4-Methylphenyl)methyl](2*H*-benzo[3,4-d]1,3-dioxolan-5-yl)}-1-(methylsulfonyl)benzene (21j): white solid; mp 153−154 °C; ^{1}H NMR ($CDCl_3$) δ 7.93 (d, J = 7.3 Hz, 2H), 7.43 (d, J = 7.4 Hz, 2H), 7.05 (d, J = 6.9 Hz, 2H), 6.86 (d, J = 7.0 Hz, 2H), 6.72 (s, 2H), 5.99 (s, 2H), 3.79 (s, 2H), 3.10 (s, 3H), 2.31 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 147.7, 147.3, 146.1, 138.9, 137.8, 135.5, 133.3, 132.0, 130.4, 129.1, 128.3, 127.1, 110.5, 109.6, 101.2, 44.5, 38.3, 20.9; LRMS (APIMS) *m/z* 398 $(M + NH_4)^+$. Anal. ($C_{22}H_{20}SO_6$) C, H.

6-(4-(Methylsulfonyl)phenyl)(2*H*-benzo[d]1,3-dioxolan-5-yl) phenyl ketone (22a): white solid; mp 180−184 °C; ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J = 8.0 Hz, 2H), 7.61 (d, J = 7.5 Hz, 2H), 7.41 (m, 3H), 7.27 (m, 2H), 7.03 (s, 1H), 6.89 (s, 1H), 6.10 (s, 2H), 2.93 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 196.8, 149.4, 147.5, 145.9, 139.0, 137.5, 134.9, 132.9, 132.8, 129.9, 129.8, 128.2, 127.2, 110.1, 109.8, 102.1, 44.4; LRMS (APIMS) *m/z* 381 $(M + H)^+$. Anal. ($C_{21}H_{16}SO_5$) C, H.

2-Fluorophenyl 6-(4-(methylsulfonyl)phenyl)(2*H*-benzo[d]1,3-dioxolan-5-yl) ketone (22b): white solid; mp 212−215 °C; ^{1}H NMR ($CDCl_3$) δ 7.74 (d, J = 6.4 Hz, 2H), 7.42−7.3 (m, 4H), 7.13 (s, 1H), 7.02 (t, J = 7.6 Hz, 1H), 6.86 (d, J = 9.3 Hz, 1H), 6.82 (s, 1H), 6.11 (s, 2H), 2.95 (s, 3H); LRMS (APIMS) *m/z* 399 $(M + H)^+$. Anal. ($C_{21}H_{15}FSO_5$) C, H.

3-Fluorophenyl 6-(4-(methylsulfonyl)phenyl)(2*H*-benzo[d]1,3-dioxolan-5-yl) ketone (22c): white solid; mp 205−209 °C; ^{1}H NMR ($CDCl_3$) δ 7.75 (d, J = 8.3 Hz, 2H), 7.38−7.30 (m, 5H), 7.24 (t, J = 5.2 Hz, 1H), 7.04 (s, 1H), 6.89 (s, 1H), 6.12 (s, 2H), 2.95 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 195.5, 163.9, 160.7, 150.0, 147.7, 145.7, 139.7, 139.2, 135.1, 132.2, 130.0, 129.9 (2 × C), 127.3 (2 × C), 125.6, 119.9 (d, J = 21 Hz), 116.4 (d, J = 22 Hz), 110.0 (d, J = 35 Hz), 102.3, 44.4; LRMS (APIMS) *m/z* 399 $(M + H)^+$, 416 $(M + NH_4)^+$. Anal. ($C_{21}H_{15}SFO_5$) C, H.

4-Fluorophenyl 6-(4-(methylsulfonyl)phenyl)(2*H*-benzo[d]1,3-dioxolan-5-yl) ketone (22d): white solid; mp 189−190 °C; ^{1}H NMR ($CDCl_3$) δ 7.73 (d, J = 8.4 Hz, 2H), 7.63 (dd, J = 8.8 and 5.3 Hz, 2H), 7.36 (d, J = 8.4 Hz, 2H), 7.0 (m, 4H), 6.1 (s, 2H), 2.94 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 195.5, 167.1, 163.8,

149.8, 147.6, 145.7, 139.7, 139.1, 134.7, 133.8, 132.5 (2 × C), 129.9 (2 × C), 127.3, 115.5, 115.2, 110.2, 109.6, 102.2, 44.4; LRMS (APIMS) *m/z* 399 $(M + H)^+$, 416 $(M + NH_4)^+$. Anal. ($C_{21}H_{15}SFO_5$) C, H.

3-Methylphenyl 6-(4-(methylsulfonyl)phenyl)(2*H*-benzo[d]1,3-dioxolan-5-yl)ketone (22e): white solid; mp 168–170 °C; ^{1}H NMR ($CDCl_3$) δ 7.75 (d, J = 8.3 Hz, 2H), 7.44–7.37 (m, 4H), 7.26–7.18 (m, 2H), 7.18 (s, 1H), 7.04 (s, 1H), 6.12 (s, 2H), 3.00 (s, 3H), 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 196.9, 149.7, 147.5, 146.0, 139.0, 138.6, 137.5, 134.9, 133.8, 133.0, 130.3, 129.9, 128.2, 127.3, 127.2, 110.2, 109.8, 102.1, 44.4, 21.2; LRMS (APIMS) *m/z* 412 $(M + NH_4)^+$, 395 $(M + H)^+$.

3-Methoxyphenyl 6-(4-(methylsulfonyl)phenyl)(2*H*-benzo[d]1,3-dioxolan-5-yl) ketone (22f): white solid; mp 158 °C; ^{1}H NMR ($CDCl_3$) δ 7.75 (d, J = 8.3 Hz, 2H), 7.39 (d, J = 8.3 Hz, 2H), 7.20–7.16 (m, 3H), 7.03 (s, 1H), 7.00–6.96 (m, 1H), 6.90 (s, 1H), 6.11 (s, 2H), 3.77 (s, 3H). 2.96 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 196.5, 159.4, 149.7, 147.4, 145.9, 139.0, 138.8, 134.9, 132.8, 129.9, 129.2, 127.2, 122.8, 119.3, 114.0, 110.1, 109.7, 102.1, 55.4, 44.4; LRMS (APIMS) *m/z* 411 $(M + H)^+$. Anal. ($C_{22}H_{18}SO_6$) C, H.

2-Fluoro-5-methylphenyl6-[4-(methylsulfonyl)phenyl]-(2*H*-benzo[d]1,3-dioxolan-5-yl) ketone (22g): white solid; mp 153–154 °C; ^{1}H NMR ($CDCl_3$) δ 7.77 (s, 1H), 7.74 (s, 1H), 7.40 (s, 1H), 7.38 (s, 1H), 7.20–7.17 (m, 1H), 7.15–7.10 (m, 2H), 6.83 (s, 1H), 6.78–6.72 (m, 1H), 6.12 (s, 2H), 2.97 (s, 3H), 2.24 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 193.4, 150.2, 147.7, 146.0, 139.1, 135.6, 134.5, 134.4, 133.8, 133.7, 131.2, 130.1, 127.0, 116.04, 115.8, 110.2, 109.8, 102.2, 44.4, 20.3; LRMS (APIMS) *m/z* 842.4 $(2M + NH_4)$, 413 $(M + H)^+$. Anal. ($C_{21}H_{15}ClO_5S$) C, H.

4-(1-(3′,5′-Difluorophenyl)-1-oxomethyl)-1,2-methylenedioxy-5-(4-methylsulfonylphenyl)benzene (22h). The compound **22h** was prepared from **20h** by method G as a white crystalline solid in 43.2% yield overall for three steps: ^{1}H NMR ($CDCl_3$) δ 7.80 (m, 2H), 7.37 (m, 2H), 7.10 (m, 2H), 7.05 (s, 1H), 6.91 (s, 1H), 6.87 (m, 1H), 6.14 (s, 2H), 2.98 (s, 3H); LRMS (APIMS) *m/z* 434 $(M + NH_4)^+$. Anal. ($C_{21}H_{14}SF_2O_5$) C, H.

3-Chlorophenyl 6-[4-(methylsulfonyl)phenyl](2*H*-benzo[d]1,3-dioxolan-5-yl) ketone (22i): white solid; mp 182–183 °C; ^{1}H NMR ($CDCl_3$) δ 7.76 (d, J = 7.7 Hz, 2H), 7.52–7.48 (m, 2H), 7.36 (d, J = 7.5 Hz, 3H), 7.28–7.20 (m, 1H), 7.06 (s, 1H), 6.91 (s, 1H), 6.13 (s, 2H), 2.96 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 195.3, 150.1, 147.7, 145.6, 139.2, 135.2, 134.3, 132.6, 132.0, 129.9 (2 × C), 129.7, 129.5, 127.7, 127.2 (2 × C), 110.1, 109.8, 102.2, 44.3; LRMS (APIMS) *m/z* 846 $(2M + NH_4)^+$, 415 $(M + H)^+$. Anal. ($C_{21}H_{15}ClO_5S$) C, H.

4-Methylphenyl 6-[4-(methylsulfonyl)phenyl](2*H*-benzo[d]1,3-dioxolan-5-yl) ketone (22j): white solid; mp 150–151 °C; ^{1}H NMR ($CDCl_3$) δ 7.75 (d, J = 8.0 Hz, 2H), 7.55 (d, J = 7.7 Hz, 2H), 7.40 (d, J = 7.9 Hz, 2H), 7.10 (d, J = 7.6 Hz, 2H), 6.90 (s, 1H), 6.82 (s, 1H), 6.10 (s, 2H), 2.96 (s, 3H), 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 196.4, 149.5, 147.4, 145.9, 144.0, 138.8, 134.8, 134.5, 133.1, 130.0, 129.8, 128.9, 127.2, 110.1, 109.6, 102.0, 44.4, 21.5; LRMS (APIMS) *m/z* 412 $(M + NH_4)$, 395 $(M + H)^+$. Anal. ($C_{22}H_{18}O_5S$) C, H.

(6-(4-Methylthiophenyl)(2*H*-benzo[d]1,3-dioxolan-5-yl))-3-pyridylmethan-1-ol (25). To a −78 °C precooled solution of 3-bromopyridine **23** (632 mg, 4 mmol) in anhydrous THF (20 mL) was added *t*-BuLi (1.7 M, 4.64 mL, 8 mmol). The resulting dark blue solution of 3-lithiopyridine **24** was stirred at −78 °C for 10 min, and then carbaldehyde **4** (820 mg, 3 mmol) in THF (15 mL) was added dropwise. The reaction mixture was then stirred at −78 °C for 30 min, slowly allowed to warm to room temperature, and stirred for an additional 30 min at room temperature. The reaction was quenched with saturated aqueous ammonium chloride solution, and the THF layer was separated. The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and filtered, and the filtrate was evaporated under reduced pressure to give the crude product. Purification by silica gel flash column chromatography using ethyl acetate/hexane (1:1) and then ethyl acetate as the eluants gave the title compound **25** (320 mg, 23% yield): mp 130–135 °C; ^{1}H NMR ($CDCl_3$) δ 8.23 (d, J = 4.3, Hz, 1H), 8.17 (s, 1H), 7.51 (d, J = 7.8 Hz, 1H), 7.18 (d, J = 8.1 Hz, 2H), 7.13 (m, 1H), 7.08 (d, J = 8.1 Hz, 2H), 6.89 (s, 1H), 6.64 (s, 1H), 5.81 (d, J = 3.0 Hz, 2H), 5.80 (s, 1H), 4.5 (br s, 1H, OH), 2.45 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 147.8, 147.7, 147.4, 146.8, 140.0, 137.6, 137.1, 134.5, 134.4, 134.2, 129.7, 126.2, 123.1, 109.8, 107.3, 101.2, 60.3, 15.6; LRMS (APIMS) *m/z* 352 $(M + H)^+$.

1-(6-(Hydroxy-3-pyridylmethyl)(2*H*-benzo[3,4-d]1,3-dioxolan-5-yl))-4-(methylsulfonyl)benzene (26). The product of the above example, **25** (501 mg, 1.45 mmol), was dissolved in MeOH (35 mL). To this solution was added Oxone (1.9 g, 2.9 mmol) in water (12 mL) dropwise. The reaction mixture was stirred at room temperature for 2 h and diluted with water, and ammonium hydroxide was added until the solution was basic. The solvent was evaporated under reduced pressure. The resulting product was extracted with ethyl acetate (3 × 50 mL), washed with brine (1 × 50 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was evaporated under reduced pressure to give the title compound **26** that was used without further purification (550 mg, 99% yield): mp 165–185 °C; ^{1}H NMR ($CDCl_3$) δ 8.32 (br s, 1H), 8.19 (s, 1H), 7.88 (d, J = 8.0 Hz, 2H), 7.50 (d, J = 7.7 Hz, 1H), 7.41 (d, J = 8.0 Hz, 2H), 7.18 (m, 1H), 6.91 (s, 1H), 6.65 (s, 1H), 5.99 (d, J = 3.0 Hz, 2H), 5.71 (s, 1H), 3.95 (br s, 1H, OH), 3.07 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 148.3, 148.2, 147.8, 147.3, 146.3, 139.5, 134.3, 134.1, 133.0, 130.5 (2 × C), 127.4 (2 × C), 123.3, 109.5, 107.8, 101.6, 69.9, 44.5; LRMS (APIMS) *m/z* 384 $(M + H)^+$.

4-(Methylsulfonyl)-1-(6-(3-pyridylmethyl)(2*H*-benzo-[3,4-d]1,3-dioxolan-5-yl))benzene (27). The hydroxyl compound **26** (540 mg, 1.41 mmol) was dissolved in anhydrous dichloromethane (5 mL), and under nitrogen atmosphere trifluoroacetic acid (10 mL) was added followed by triethylsilane (5 mL). The reaction mixture was stirred at room temperature overnight. The solvent and trifluoroacetic acid were evaporated under reduced pressure, and the residue was extracted with dichloromethane. The combined organic extracts were washed with water and brine, dried over sodium sulfate, and filtered. The filtrate was evaporated under reduced pressure to give the crude product that was purified by silica gel column chromatography using 5% methanol in dichloromethane as the eluant to give the title compound as a white solid **27** (255 mg, 41% yield): mp 121–137 °C; ^{1}H NMR ($CDCl_3$) δ 8.38 (d, J = 4.0 Hz, 1H), 8.17 (s, 1H), 7.90 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 8.2 Hz, 2H), 7.21 (d, J = 7.9 Hz, 1H), 7.12 (dd, J = 7.8 and 4.5 Hz, 1H), 6.7 (s, 1H), 6.68 (s, 1H), 5.99 (s, 2H), 3.81 (s, 2H), 3.08 (s, 3H); LRMS (APIMS) *m/z* 368 $(M + H)^+$. Anal. ($C_{20}H_{17}SNO_4$) C, H.

6-(4-(Methylsulfonyl)phenyl)(2*H*-benzo[d]1,3-dioxolan-5-yl) 3-Pyridyl Ketone (28). A suspension of the hydroxyl compound **26** (80 mg, 0.209 mmol) and alumina (1 g) in anhydrous CH_2Cl_2 (10 mL) was stirred at room temperature. To this mixture was added pyridinium chlorochromate (48 mg, 0.21 mmol), and the mixture was stirred at room temperature for 15 min. The reaction mixture was diluted with CH_2Cl_2, and the alumina was removed by filtration. The filtrate was washed with water (3 × 25 mL), saturated aqueous sodium bicarbonate (2 × 25 mL), and brine (1 × 25 mL) and then dried over anhydrous sodium sulfate and filtered. The filtrate was evaporated under reduced pressure. Purification by flash column chromatography using ethyl acetate as the eluant gave the title compound **28** as a white solid (110 mg, 96.5% yield): mp 186–190 °C; ^{1}H NMR ($CDCl_3$) δ 8.70 (br s, 1H), 8.59 (br s, 1H), 7.91 (d, J = 7.5 Hz, 1H), 7.75 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.0 Hz, 2H), 7.25 (br s, 1H), 7.09 (s, 1H), 6.98 (s, 1H), 6.14 (s, 2H), 2.94 (s, 3H); LRMS (APIMS) *m/z* 382 $(M + H)^+$.

4-Methyl-3-pyridyl 6-[4-(methylsulfonyl)phenyl](2*H*-benzo[d]1,3-dioxolan-5-yl) ketone (31): white solid; mp 192–194 °C; ^{1}H NMR ($CDCl_3$) δ 8.23 (d, J = 3.9 Hz, 1H), 7.70 (d, J = 7.9 Hz, 2H), 7.35 (d, J = 7.8 Hz, 2H), 7.16 (s, 1H), 7.07 (m, 1H), 6.78 (s, 1H), 6.08 (s, 2H), 2.95 (s, 3H). 2.37 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 196.6, 154.0, 150.3, 147.8, 146.7, 145.8, 138.9, 136.3, 134.2, 133.3, 129.7 (2 × C), 128.2, 126.7 (2 × C), 125.1, 110.4, 110.0, 102.2, 44.4, 19.0; LRMS (APIMS) *m/z* 396 $(M + H)^+$. Anal. ($C_{21}H_{17}SNO_5$) C, H.

4-Bromo-3-pyridyl 6-[4-(methylsulfonyl)phenyl](2*H*-benzo[d]1,3-dioxolan-5-yl) ketone (35): white solid; mp 180−190 °C; ^{1}H NMR ($CDCl_3$) δ 8.10 (m, 2H), 7.76 (d, J = 7.8 Hz, 2H), 7.36 (d, J = 7.8 Hz, 2H), 7.3−7.2 (m, 1H), 7.2 (s, 1H), 6.81 (s, 1H), 6.15 (s, 2H), 3.10 (s, 3H); LRMS (APIMS) m/z 460 (M + H)$^+$, 462 (M + 2 + H)$^+$. Anal. ($C_{20}H_{14}BrSNO_5$) C, H.

4-(Methylsulfonyl)-1-[6-(piperidylmethyl)(2*H*-benzo-[3,4-d]1,3-dioxolan-5-yl)]benzene (38a). Compound **38a** was prepared by alkylation of piperidine **37a** with chloromethyl compound **16** using method H. Pure product **38a** was obtained as white solid in 69% yield: mp 138−141 °C; ^{1}H NMR ($CDCl_3$) δ 7.93 (d, J = 8.3 Hz, 2H), 7.58 (d, J = 8.4 Hz, 2H), 7.25 (s, 1H), 7.03 (s, 1H), 5.98 (s, 2H), 3.17 (s, 2H). 3.10 (s, 3H), 2.23 (m, 4H), 1.47 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 147.4, 147.3, 146.4, 138.7, 133.9, 130.6, 130.5, 130.5, 126.8, 110.3, 109.6, 101.2, 60.4, 54.0, 45.5, 26.0, 24.3; LRMS (APIMS) m/z 374 (M + H)$^+$. Anal. ($C_{20}H_{23}SNO_4$) C, H.

Ethyl 1-({6-[4-(Methylsulfonyl)phenyl]-2*H*-benzo[d]1,3-dioxolan-5-yl}methyl)piperidine-3-carboxylate (38b). Compound **38b** was prepared by alkylation of 3-(carboxyethyl)-piperidine **37b** with chloromethyl compound **16** using method H. Pure product **38b** was obtained as white solid in 93% yield: mp 144−145 °C; ^{1}H NMR ($CDCl_3$) δ 7.93 (d, J = 8.3 Hz, 2H), 7.54 (d, J = 8.3 Hz, 2H), 7.01 (s, 1H), 6.67 (s, 1H), 5.98 (s, 2H), 4.05 (q, J = 7.2 Hz, 2H), 3.22 (s, 2H), 3.09 (s, 3H), 2.74 (m, 1H), 2.53 (m, 2H), 2.2 (m, 1H), 1.95 (m, 2H), 1.80 (m, 1H), 1.65 (m, 2H), 1.18 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.1, 147.5, 147.2, 146.5, 138.8, 133.8, 130.5, 129.9, 126.9, 110.1, 109.6, 101.2, 60.2, 59.9, 54.8, 53.3, 45.5, 41.8, 26.8, 24.5. 14.1; LRMS (APIMS) m/z 446 (M + H)$^+$. Anal. ($C_{23}H_{27}SNO_6$) C, H.

Ethyl 1-({6-[4-(Methylsulfonyl)phenyl]-2*H*-benzo[d]1,3-dioxolan-5-yl}methyl)piperidine-4-carboxylate (38c). Compound **38c** was prepared by alkylation of 4-(carboxyethyl)-piperidine **37c** with chloromethyl compound **16** using method H. Pure product **38c** was obtained as white solid in 94% yield: mp 121−122 °C; ^{1}H NMR ($CDCl_3$) δ 7.92 (d, J = 8.3 Hz, 2H), 7.55 (d, J = 8.3 Hz, 2H), 7.0 (s, 1H), 6.67 (s, 1H), 5.98 (s, 2H), 4.09 (q, J = 7.1 Hz, 2H), 3.19 (s, 2H), 3.09 (s, 3H), 2.69 (m, 2H), 2.1 (m, 1H), 1.8−1.5 (m, 6H), 1.21 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 175.1, 147.5, 147.2, 146.5, 138.8, 133.9, 130.5 (2 × C), 130.1, 126.9 (2 × C), 110.2, 109.6, 101.2, 60.2, 58.9, 52.4 (2 × C), 44.5, 41.0, 28.3 (2 × C), 14.2; LRMS (APIMS) m/z 446 (M + H)$^+$. Anal. ($C_{23}H_{27}SNO_6$) C, H.

1-{6-[(4-Hydroxypiperidyl)methyl](2*H*-benzo[3,4-d]1,3-dioxolan-5-yl)}-4-(methylsulfonyl)benzene (38d). Compound **38d** was prepared by alkylation of 4-hydroxypiperidine **37d** with chloromethyl compound **16** using method H. Pure product **38d** was obtained as white solid in 90% yield: mp 76−82 °C; ^{1}H NMR ($CDCl_3$) δ 7.92 (d, J = 7.0 Hz, 2H), 7.55 (d, J = 7.1 Hz, 2H), 7.01 (s, 1H), 6.67 (s, 1H), 5.98 (s, 2H), 3.62 (m, 1H), 3.20 (s, 2H). 3.09 (s, 3H), 2.59 (m, 2H), 1.99 (m, 2H), 1.8−1.4 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 147.5, 147.3, 146.5, 138.8, 133.9, 130.6, 130.2, 126.9, 110.2, 109.7, 101.3, 67.9, 59.5, 50.5, 44.5, 34.5; LRMS (APIMS) m/z 390 (M + H)$^+$. Anal. ($C_{20}H_{23}SNO_5$) C, H.

1-(6-{[2-(Hydroxymethyl)piperidyl]methyl}(2*H*-benzo-[3,4-d]1,3-dioxolan-5-yl))-4-(methylsulfonyl)benzene (38e). Compound **38e** was prepared by alkylation of 2-(hydroxymethyl)piperidine **37e** with chloromethyl compound **16** using method H. Pure product **38e** was obtained as white solid in 81% yield: mp 127−137 °C; ^{1}H NMR ($CDCl_3$) δ 7.93 (d, J = 6.5 Hz, 2H), 7.53 (d, J = 6.5 Hz, 2H), 7.00 (s, 1H), 6.67 (s, 1H), 5.98 (s, 2H), 3.85 (d, J = 13.6 Hz, 1H), 3.57 (dd, J = 11 and 4.1 Hz, 1H), 3.37 (dd, J = 11 and 4.1 Hz, 1H), 3.18 (d, J = 13.6 Hz, 1H), 3.1 (s, 3H), 2.63 (m, 1H), 2.42 (m, 1H), 2.00−1.20 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 147.6, 147.4, 146.5, 138.8, 133.9, 130.5, 130.1, 126.9, 110.2, 109.7, 101.3, 66.6, 60.4, 56.9, 53.8, 44.5, 38.2, 27.2, 24.6; LRMS (APIMS) m/z 404 (M + H)$^+$. Anal. ($C_{21}H_{25}SNO_5$) C, H.

1-(6-((3-(Hydroxymethyl)piperidyl)methyl)(2*H*-benzo-[3,4-d]1,3-dioxolan-5-yl))-4-(methylsulfonyl)benzene (38f). The chloromethyl compound **16** (410 mg, 1.2 mmol) and 2-piperidine methanol **37f** (138 mg, 1.2 mmol) were dissolved in anhydrous DMF (5 mL). Potassium carbonate (830 mg, 6 mmol) was added, and reaction mixture was stirred at room temperature overnight. The reaction mixture was then treated with ice-cold water and extracted with ethyl acetate (2 × 75 mL). The combined organic extracts were washed with water (1 × 50 mL) and brine (1 × 50 mL), dried over sodium sulfate, and filtered. The filtrate was evaporated under reduced pressure to give the crude product that was purified by flash column chromatography using methanol:dichloromethane (5:95) as an eluent to give the title compound **38f** as a white solid (410 mg, 80% yield): mp 127−137 °C; ^{1}H NMR ($CDCl_3$) δ 7.92 (d, J = 6.4 Hz, 2H), 7.56 (d, J = 6.4 Hz, 2H), 7.26 (s, 1H), 6.67 (s, 1H), 5.98 (s, 2H), 3.45 (m, 2H), 3.21 (s, 2H). 3.10 (s, 3H), 2.63 (m, 1H), 2.42 (m, 1H), 1.90−1.07 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 147.5, 147.4, 146.6, 138.8, 134.0, 130.5, 130.2, (2 × C), 127.0 (2 × C), 110.2, 109.7, 101.3, 66.7, 60.4, 56.9, 53.8, 44.6, 38.2, 27.3, 24.6; LRMS (APIMS) m/z 404 (M + H)$^+$. Anal. ($C_{21}H_{25}SNO_5$) C, H.

(6-(4-Methylthiophenyl)-2*H*-benzo[d]1,3-dioxolan-5-yl)-methylamine (39). To a stirred mixture of carbaldehyde **4** (2.72 g, 10 mmol), 4 A molecular sieves (6 g), and NH_4OAc (11.6 g, 150 mmol) in MeOH (80 mL) was added sodium cyanoborohydride (0.95 g, 15 mmol). The reaction mixture was stirred at room temperature for 4 days and filtered, and the filtrate was evaporated under reduced pressure. The resulting residue was dissolved in EtOAc (200 mL), washed with 2 M aqueous sodium carbonate, dried over sodium sulfate, and filtered. The filtrate was evaporated under reduced pressure. The crude product obtained was purified by flash chromatography using MeOH:CH_2Cl_2 (1:9) with a trace amount of NH_4OH as the eluant to give the title compound **39** as a viscous oil which solidified on standing (1.70 g, 62% yield): mp 42 °C; ^{1}H NMR ($CDCl_3$) δ 7.28 (dd, J = 6.5, 1.8 Hz, 2H), 7.20 (dd, J = 6.5, 1.8 Hz, 2H), 6.94 (s, 1H), 6.69 (s, 1H), 5.96 (s, 2H), 3.67 (s, 2H), 2.51 (s, 3H), 1.53 (br, 2H); LRMS (APIMS) m/z 274 (M + H)$^+$.

1-((6-(4-Methylsulfonyl)phenyl)-2*H*-benzo[d]1,3-dioxolan-5-yl)methyl)piperidin-2-one (42). Lactam **41** was prepared by alkylation of **39** with bromo ester **40**, and subsequently **41** was oxidized to give **42** using method C. Pure product **42** was obtained as white prisms (108 mg, 70% yield): mp 156−157 °C; ^{1}H NMR ($CDCl_3$) δ 7.97 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.4 Hz, 2H), 6.81 (s, 1H), 6.68 (s, 1H), 6.01 (s, 2H), 4.47 (s, 2H), 3.11 (s, 3H), 2.95 (t, J = 6.0 Hz, 2H), 2.38 (t, J = 6 0 Hz, 2H), 1.75−1.71 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 169.9, 148.2, 146.8, 146.4, 139.3, 133.4, 130.4, 128.4, 127.4, 109.6, 107.9, 101.4, 47.1, 44.5, 32.3, 23.1, 21.3; LRMS (APIMS) m/z 388 (M + H)$^+$. Anal. ($C_{20}H_{21}SNO_5$) C, H, N, S.

6-[4-(Methylsulfonyl)phenyl](2*H*-benzo[d]1,3-dioxolen-5-yl) Pyrrolidinyl Ketone (45a). Acid chloride **43b** was prepared from 6-[4-(methylsulfonyl)phenyl]-2*H*-benzo[*d*]1,3-dioxolene-5-carboxylic acid **43a** and it was reacted with pyrrolidine using method H to yield pure product **45a** in 57% yield as a white solid: mp 189−192 °C; ^{1}H NMR ($CDCl_3$) δ 7.94 (d, J = 8.5 Hz, 2H), 7.65 (d, J = 8.5 Hz, 2H), 6.91 (s, 1H), 6.87 (s, 1H), 6.06 (s, 2H), 3.37 (t, J = 7.0 Hz, 2H), 3.08 (s, 3H), 2.79 (t, J = 7.0 Hz, 2H), 1.67 (quin., J = 7.0 Hz, 2H), 1.54 (quin., J = 7.0 Hz, 2H); LRMS (APIMS) m/z 374 (M + H)$^+$. Anal. ($C_{19}H_{19}SNO_5$) C, H.

6-[4-(Methylsulfonyl)phenyl](2*H*-benzo[d]1,3-dioxolen-5-yl) Piperidyl Ketone (45b). Acid chloride **43b** was prepared from 6-[4-(methylsulfonyl)phenyl]-2*H*-benzo[*d*]1,3-dioxolene-5-carboxylic acid **43a** and it was reacted with piperidine using method H to yield pure product **45b** in 55% yield as a white solid: mp 152−154 °C; ^{1}H NMR ($CDCl_3$) δ 7.95 (d, J = 8.5 Hz, 2H), 7.64 (d, J = 8.5 Hz, 2H), 6.87 (s, 1H), 6.86 (s, 1H), 6.06 (d, J = 3.9 Hz, 2H), 3.56 (m, 1H), 3.36 (m, 1H), 3.07 (s, 3H), 3.03 (m, 1H), 2.71 (m, 1H), 1.48−1.23 (m, 5H), 0.77 (m, 1H); LRMS (APIMS) m/z 388 (M + H)$^+$. Anal. ($C_{20}H_{21}SNO_5$) C, H.

4-Methylpiperazinyl 6-[4-(Methylsulfonyl)phenyl](2*H*-benzo[d]1,3-dioxolen-5-yl) Ketone (46a). Acid chloride **43b** was prepared from 6-[4-(methylsulfonyl)phenyl]-2*H*-benzo[*d*]-1,3-dioxolene-5-carboxylic acid **43a** and it was reacted with

N-methylpiperazine using method H to yield pure product **46a** in 80% yield as a white solid: mp 204−206 °C.; ^{1}H NMR ($CDCl_3$) δ 7.96 (d, J = 8.3 Hz, 2H), 7.63 (d, J = 8.3 Hz, 2H), 6.88 (s, 1H), 6.86 (s, 1H), 6.06 (s, 2H), 3.55 (t, J = 5.0 Hz, 2H), 3.09 (s, 3H), 3.04 (m, 1H), 2.82 (m, 1H), 2.32 (m, 1H), 2.11 (s, 3H), 2.04 (m, 1H), 1.97 (m, 1H), 1.41 (m, 1H); LRMS (APIMS) m/z 403 $(M + H)^+$.

6-[4-(Methylsulfonyl)phenyl](2*H*-benzo[d]1,3-dioxolen-5-yl) Morpholin-4-yl Ketone (46b). Acid chloride **43b** was prepared from 6-[4-(methylsulfonyl)phenyl]-2*H*-benzo[*d*]1,3-dioxolene-5-carboxylic acid **43a** and it was reacted with morpholine using method H to yield pure product **46b** in 92% yield as a white solid: mp 203−205 °C; ^{1}H NMR ($CDCl_3$) δ 7.98 (d, J = 8.5 Hz, 2H), 7.63 (d, J = 8.5 Hz, 2H), 6.89 (s, 1H), 6.86 (s, 1H), 6.07 (s, 2H), 3.59 (m, 2H), 3.45 (m, 1H), 3.32 (m, 2H), 3.09 (s, 3H), 3.04 (m, 1H), 2.76 (m, 2H); LRMS (APIMS) m/z 390 $(M + H)^+$. Anal. ($C_{19}H_{19}SNO_6$) C, H.

5-[4-(Aminosulfonyl)phenyl]-4-benzyl-1,2-methylenedioxybenzene (47). 4-Benzyl-1,2-methylenedioxy-5-(4-methylsulfonylphenyl)benzene **21a** (152 mg, 0.419 mmol) was dissolved in dry THF (0.7 mL) in an oven-dried 25 mL single necked round-bottom flask which had been cooled to ambient temperature under argon. The flask was placed in a water bath and *n*-BuLi (1.2 equiv, 0.503 mmol, 0.3 mL of a 1.6 M solution in hexanes) was added, generating a dark yellow solution. The reaction mixture was stirred at ambient temperature for 0.5 h and then to the solution was added chloromethyltrimethylsilane (78 mg, 1.5 equiv, 0.635 mmol, 0.09 mL) in one portion. The orange reaction mixture was stirred at ambient temperature for 4 h, at which point TLC (3:7 EtOAc:hexanes) indicated the reaction to be complete. Tetrabutylammonium fluoride (5.4 equiv, 2.27 mmol, 2.27 mL of a 1 M solution in THF) was then added, generating a clear dark solution. The reaction flask was fitted with a reflux condenser and heated to the reflux temperature for 0.5 h. The reaction was cooled to ambient temperature and to the reaction mixture was added sequentially NaOAc (189 mg, 5.5 equiv, 2.31 mmol), H_2O (7 mL), and hydroxylamine-*O*-sulfonic acid (269 mg, 5.7 equiv, 2.38 mmol). The reaction mixture was stirred at ambient temperature overnight at which point TLC (3:7 EtOAc:hexanes) showed the reaction to be complete. The reaction mixture was poured into a separatory funnel and diluted with 15 mL of EtOAc, and the aqueous layer was removed. The organic layer was sequentially washed with saturated aqueous $NaHCO_3$ (2 × 7 mL), water (1 × 7 mL), and brine (1 × 7 mL). The organic layer was dried over Na_2SO_4, the reaction mixture filtered, and the solvent removed in vacuo, affording a brown oil. The oil was chromatographed on two 20 × 20 cm, 1 mm thick Alltech silica gel plates eluting once with methylene chloride and then once with 3:97 EtOAc:CH_2Cl_2. The desired band was scraped from the plates and extracted into CH_2Cl_2, affording 65 mg (43% yield) of the sulfonamide **47** as a white solid: mp 165−167 °C; ^{1}H NMR ($CDCl_3$) δ 7.89 (m, 2H), 7.36 (m, 2H), 7.20 (m, 3H), 6.95 (m, 2H), 6.70 (m, 2H), 5.98 (s, 2H), 4.79 (br s, 2H), 3.82 (s, 2H); LRMS (APIMS) m/z 385 $(M + NH_4)^+$. Anal. ($C_{20}H_{17}SNO_4$) C, H.

7-Methylthio-5-phenyl-2*H*-fluoreno[2,3-d]1,3-dioxolane (48). Treatment of compound **19a** under the conditions described in method F resulted in the formation of **48** in nearly quantitative yield: white solid; mp 173−175 °C; ^{1}H NMR ($CDCl_3$) δ 7.50 (d, J = 8.0 Hz, 2H), 7.30−7.00 (m, 7H), 6.70 (s, 1H), 5.96 (s, 2H), 4.80 (s, 1H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 148.8, 147.7, 147.5, 141.7, 141.2, 138.8, 136.0, 134.4, 128.8 (2 × C), 128.3 (2 × C), 127.0, 126.3, 123.9, 119.2, 106.1, 101.3, 100.3, 54.1, 16.6.

4-Methylthio-1-[6-benzyl(2*H*-benzo[3,4-d]1,3-dioxolan-5-yl)]benzene (49a). Compound **19a** was hydrogenated overnight at 40 psi using method E to furnish **49a** as a white solid in 71% yield: mp 86−87 °C; ^{1}H NMR ($CDCl_3$) δ 7.25 (m, 7H), 7.00 (d, J = 8.5 Hz, 2H), 6.73 (s, 1H), 6.67 (s, 1H), 5.95 (s, 2H), 3.85 (s, 2H), 2.53 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 147.1, 145.9, 141.7, 138.4, 137.1, 135.0, 131.8, 130.0 (2 × C), 128.8 (2 × C), 128.4 (2 × C) 126.4 (2 × C), 126.3, 125.9, 110.3, 101.1, 38.9, 16.0.

Fluoro({4-[6-benzyl(2*H*-benzo[3,4-d]1,3-dioxolan-5-yl)]-phenyl}sulfonyl)methane (50). (Fluoromethyl) sulfone **50** was prepared in a two-step procedure. In a 25 mL two-neck round-bottom flask, to a solution of [bis(2-methoxyethyl)amino] sulfur trifluoride (130 μL) in anhydrous dichloromethane (2 mL) was added solution of **49a** (134 mg, 0.4 mmol) in dichloromethane (1 mL), followed by catalytic amount of $SbCl_3$ (5 mg). The reaction mixture was stirred at room temperature overnight. It was then diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The organic layer was separated and concentrated to approximately 10 mL, to this solution was added 98% *m*-chloroperbenzoic acid (178 mg) (1 mmol), and the mixture stirred at room temperature for 2 h. The resulting mixture was diluted with CH_2Cl_2 (50 mL), washed with 2 M aqueous sodium bicarbonate, dried over sodium sulfate, and filtered. The filtrate was evaporated under reduced pressure. The crude product obtained was purified by flash chromatography using EtOAc:hexanes (1:1) as the eluant to give the title compound **50** as a white solid (52 mg, 36% yield): mp 142−143 °C; ^{1}H NMR ($CDCl_3$) δ 7.64 (d, J = 8.1 Hz, 2H), 7.40 (d, J = 8.1 Hz, 2H), 7.20 (m, 2H), 6.94 (d, J = 7.0 Hz, 2H), 6.71 (s, 2H), 5.98 (s, 2H), 5.2 (dd, J = 9.0 and 4.0 Hz, 1H), 5.0 (dd, J = 9.0 and 4.0 Hz, 1H), 3.82 (s, 2H); LRMS (APIMS) m/z 385 $(M + H)^+$.

2-(4-Methylthiophenyl)benzaldehyde (52). Compound **52** was prepared using **51** and **3** by method A. The title compound **52** was obtained as colorless thick oil in 96% yield: ^{1}H NMR ($CDCl_3$) δ 9.98 (s, 1H), 8.01 (dd, J = 7.8 and 1.2 Hz, 1H), 7.60 (dt, J = 7.5 and 1.4 Hz, 2H), 7.62−7.40 (m, 2H), 7.30−7.25 (m, 3H), 2.53 (s, 3H); LRMS (APIMS) m/z 229 $(M + H)^+$.

(2-(4-Methylthiophenyl)phenyl)methan-1-ol (53). The product of the above example was converted to **53** by method I. The title compound was obtained as a white solid in 97% yield: mp 81−85 °C; ^{1}H NMR ($CDCl_3$) δ 7.55 (m, 1H), 7.40−7.20 (m, 7H), 4.61 (s, 2H), 2.50 (s, 3H), 1.63 (br s, 1H, OH); LRMS (APIMS) m/z 248 $(M + NH_4)^+$.

1-(2-(Hydroxymethyl)phenyl)-4-(methylsulfonyl)benzene (54). Compound **54** was prepared by method C in 89% yield: mp 123−124 °C; ^{1}H NMR ($CDCl_3$) δ 8.02 (d, J = 8.2 Hz, 2H), 7.65 (d, J = 8.2 Hz, 2H), 7.62 (s, 1H), 7.52−7.41 (m, 2H), 7.31 (d, J = 8.2 Hz, 1H), 4.60 (s, 2H), 3.15 (s, 3H), 2.10 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 146.5, 139.4, 139.2, 137.8, 130.2 (2 × C), 129.8, 129.0, 128.7, 127.9, 127.2 (2 × C), 62.7, 44.5; LRMS (APIMS) m/z 280 $(M + NH_4)^+$.

2-(4-(Methylsulfonyl)phenyl)benzaldehyde (55). The product of the above example **54** was oxidized to **55** by method G. The title compound **55** was obtained as a white solid in 64% yield: mp 115−116 °C; ^{1}H NMR ($CDCl_3$) δ 9.99 (s, 1H), 8.09 (m, 3H), 7.73 (t, J = 7.3 Hz, 1H), 7.63 (m, 3H), 7.46 (d, J = 7.4 Hz, 1H), 3.17 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 191.1, 143.7, 143.3, 140.2, 133.8, 133.6, 130.8 (2 × C), 130,6, 129.8, 128.5, 127.4 (2 × C) 44.5; LRMS (APIMS) m/z 278 $(M + NH_4)^+$.

1-(2-(Cyclohexylidenemethyl)phenyl)-4-(methylsulfonyl)benzene (56). Compound **56** was prepared by method B using cyclohexyltriphenylphosphonium bromide **5b** and **55**. The title compound was obtained as a white powder 35% yield: mp 83 °C; ^{1}H NMR ($CDCl_3$) δ 8.00 (d, J = 7.9 Hz, 2H), 7.63 (d, J = 7.9 Hz, 2H), 7.33 (m, 4H), 6.01 (s, 1H), 3.15 (s, 3H), 2.21 (m, 4H), 1.60−1.46 (m, 6H); LRMS (APIMS) m/z 344 $(M + NH_4)^+$. Anal. ($C_{20}H_{22}SO_2$) C, H.

(3-Fluorophenyl)(2-(4-methylthiophenyl)phenyl)-methan-1-ol (57). The Grignard reagent was prepared by refluxing 1-bromo-3-fluorobenzene and was reacted with carbaldehyde **4** by method D to give the title compound **57** as colorless thick oil in 98% yield: ^{1}H NMR ($CDCl_3$) δ 7.47 (d, J = 7.1 Hz, 1H), 7.40−7.18 (m, 8H), 6.90 (m, 3H), 5.91 (d, J = 3.6 Hz, 1H), 2.52 (s, 3H), 2.25 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 164.4, 161.1, 146.4, 140.7, 140.6, 137.7, 137.3, 130.1, 129.7 (2 × C), 129.6, 128.0, 127.7, 127.3, 126.3 (2 × C), 122.1, 114.0 (d, J = 21 Hz), 113.5 (d, J = 22 Hz), 71.8, 15.8; LRMS (APIMS) m/z 342 $(M + NH_4)^+$.

1-(2-((3-Fluorophenyl)hydroxymethyl)phenyl)-4-(methylsulfonyl)benzene (58). The (methylthio) compound

57 (220 mg, 0.679 mmol) was dissolved in dichloromethane (20 mL). Saturated aqueous sodium bicarbonate (5 mL) was added, followed by recrystallized *m*-chlorobenzoic acid (302 mg, 1.69 mmol, 98% yield), and the reaction mixture was stirred at room temperature for 2 h. The organic layer was separated. The aqueous layer was extracted with dichloromethane, and the combined organic layers were washed with 10% sodium bicarbonate (3 × 25 mL), water (1 × 25 mL), and brine (1 × 25 mL), dried over sodium sulfate, and filtered. The filtrate was evaporated under reduced pressure to give the crude product. Trituration with 10% ethyl acetate in hexane gave the title compound as a white solid that was recrystallized from hexane (190 mg, 79% yield): mp 117−119 °C; ^{1}H NMR ($CDCl_3$) δ 7.99 (d, J = 8.2 Hz, 2H), 7.62 (d, J = 7.6 Hz, 1H), 7.51 (d, J = 8.2 Hz, 2H), 7.44 (m, 2H), 7.31−7.20 (m, 2H), 7.00−6.70 (m, 3H), 5.86 (s, 2H), 3.15 (s, 3H), 2.35 (br s, 1H, OH); LRMS (APIMS) *m/z* 374 $(M + NH_4)^+$.

1-(2-((3-Fluorophenyl)methyl)phenyl)-4-(methylsulfonyl)benzene (59a). Compound **59a** was prepared from **58** by method F. The title compound **59a** was obtained as a white solid in 83% yield: mp 97−98 °C; ^{1}H NMR ($CDCl_3$) δ 7.97 (d, J = 8.3 Hz, 2H), 7.45 (d, J = 8.3 Hz, 2H), 7.45−7.15 (m, 5H), 6.98 (dt, J = 8.4 and 2.2 Hz, 1H), 6.75 (d, J = 7.6 Hz, 1H), 6.63 (d, J = 10 Hz, 1H), 3.97 (s, 2H), 3.15 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 164.4, 161.2, 147.2, 143.3 (d, J = 7 Hz), 140.3, 139.2, 137.2, 130.7, 130.1 (2 × C), 129.9, 129.7 (d, J = 2.5 Hz), 128.6, 127.1 (2 × C), 126.9, 124.3 (d, J = 2.5 Hz), 115.4 (d, J = 21 Hz), 112.9 (d, J = 21 Hz), 44.5, 38.9; LRMS (APIMS) *m/z* 358 $(M + NH_4)^+$. Anal. ($C_{20}H_{17}SFO_2$) C, H.

3-Fluorophenyl 2-(4-(Methylsulfonyl)phenyl)phenyl Ketone (60a). Compound **58** was converted to **60a** by method G to give the title compound **60a** as a white crystalline solid in 79% yield: mp 105−106 °C; ^{1}H NMR ($CDCl_3$) δ 7.79 (d, J = 8.1 Hz, 2H), 7.35−7.15 (m, 10H), 2.83 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 196.4, 164.0, 160.7, 145.7, 139.3, 138.2, 131.0, 130.2, 130.1, 130.0, 129.8 (2 × C), 129.1, 128.2, 127.7 (2 × C), 125.7 (d, J = 12 Hz), 120.1 (d, J = 22 Hz), 116.3 (d, J = 22 Hz), 44.4; LRMS (APIMS) *m/z* 372 $(M + NH_4)^+$. Anal. ($C_{20}H_{15}SFO_3$) C, H.

1-[6-(3,5-Difluorophenyl)(2*H*-benzo[3,4-d]1,3-dioxolan-5-yl)]-4-(methylsulfonyl)benzene (65). Compound **65** was prepared from carbaldehyde **61** in three steps. Suzuki coupling reaction of **61** with 4-(methylthio)phenylboronic acid **3** using standard conditions as described in method A gave the product **62** after purification by column chromatography. Another Suzuki coupling reaction of **62** with 3,5-difluoro-4-(methylthio)-phenylboronic acid **63** using method A gave the methylthio compound **64**, which was oxidized with Oxone using method C to afford the desired product **65** as a white solid (three steps overall 26% yield): mp 195−198 °C; ^{1}H NMR ($CDCl_3$) δ 7.79 (d, J = 8.3 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 6.86 (m, 2H), 6.7−6.5 (m, 3H), 6.02 (s, 2H), 3.05 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 164.2, 160.9, 148.0, 146.5, 143.9, 138.7, 132.4, 130.6, 127.2, 113.0 (d, J = 8 Hz), 112.8, 110.4, 102.4 (t, J = 25.2 Hz), 101.8, 44.5; LRMS (APIMS) *m/z* 406 $(M + NH_4)^+$. Anal. ($C_{20}H_{23}SNO_4$) C, H.

4-(Methylsulfonyl)-1-[6-(3-phenylpropyl)(2*H*-benzo[3,4-d]1,3-dioxolan-5-yl)]benzene (67). Compound **67** was prepared from carbaldehyde **4** in three steps. First, carbaldehyde **4** was treated with (phenethyl)magnesium chloride according to method D, the product obtained was oxidized with Oxone using method C, and then deoxygenation was performed using method E to give the desired product as a white solid: mp 110−114 °C; ^{1}H NMR ($CDCl_3$) δ 7.9 (d, J = 8.1 Hz, 2H), 7.40 (d, J = 8.1 Hz, 2H), 7.25 (m, 3H), 7.00 (d, J = 6.8 Hz, 2H), 6.80 (s, 1H), 6.63 (s, 1H), 5.97, (s, 2H), 3.1 (s, 3H), 2.47 (m, 4H), 1.76 (m, 2H); LRMS (APIMS) *m/z* 412 $(M + NH_4)^+$. Anal. ($C_{23}H_{22}SO_4$) C, H.

4,5-Dimethoxy-2-(4-methylthiophenyl)benzaldehyde (69). Compound **69** was prepared by the reaction of 2-bromoveratraldehyde **68** (25 g, 103.3 mmol) and 4-(methylthio)-benzeneboronic acid **3** (19.66 g, 118.5 mmol) in toluene (550 mL) and sodium carbonate (2 M, 103 mL, 206 mmol) using standard conditions for Suzuki cross-coupling reaction as described in method A. The product was purified by trituration with ethyl acetate:hexane to give the title compound as a white solid (21.3 g, 85% yield): mp 114−115 °C; ^{1}H NMR ($CDCl_3$) δ 9.83 (s, 1H), 7.64 (s, 1H), 7.43−7.23 (m, 4H), 6.83 (s, 1H), 3.98 (d, J = 2.4 Hz, 6H), 2.55 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 190.9, 153.4, 148.7, 140.8, 138.9, 134.1, 130.5, 126.9, 126.1, 112.5, 108.7, 56.2, 56.1, 15.6; LRMS (APIMS) *m/z* 289 $(M + H)^+$.

4-(1-(3′,5′-Difluorophenyl)-1-hydroxymethyl)-1,2-dimethoxy-5-(4-methylthiophenyl)benzene (70). Grignard reagent **17h** was prepared by refluxing magnesium metal (2.21 g, 91.06 mmol), dry THF (200 mL), and 3,5-difluorobromobenzene (11.04 mL, 95.85 mmol) and reacted with carbaldehyde **69** (91 mmol) using method D. The crude product obtained was oxidized using method C to afford the desired product **70** that was used without further purification.

5-(1-(3′,5′-Difluorophenyl)methyl)-1,2-dimethoxy-4-(4-methylsulfonylphenyl)benzene (72). Product **70** was oxidized using Oxone by method C to give methyl sulfone **71**, and the crude product **71** obtained was subsequently deoxygenated using method F to yield the title compound **72** as a white solid (18.74 g, 93.4% overall yield for the three steps from **70**): mp 157−159°C; ^{1}H NMR ($CDCl_3$) δ 7.92 (m, 2H), 7.40 (m, 2H), 6.75 (s, 1H), 6.73 (s, 1H), 6.59 (m, 1H), 6.44 (m, 2H), 3.89 (s, 6H), 3.86 (s, 2H), 3.09 (s, 3H); LRMS (APIMS) *m/z* 436 $(M + NH_4)^+$. Anal. ($C_{22}H_{20}SF_2O_4$) C, H.

5-(1-(3′,5′-Difluorophenyl)methyl)-1,2-dihydroxy-4-(4-methylsulfonylphenyl)benzene (73). Dimethoxy compound **72** (18.74 g, 44.78 mmol) was dissolved in dry CH_2Cl_2 (500 mL) and cooled to 0 °C, and boron tribromide (0.112 mol, 10.6 mL) was added over a period of 2−3 min. The resulting solution was stirred at 0 °C for 45 min. The reaction was quenched at 0 °C by the addition of MeOH (70 mL) followed a minute later by the addition of water (70 mL). The reaction mixture was warmed to room temperature. The solvent (CH_2Cl_2 and MeOH) was evaporated under reduced pressure to give a solid. The solid was removed by filtration, washed with water, and then dried under high vacuum overnight to give the title compound **73** as a pale yellow solid (17.0 g, 97.2% yield): mp 214°C (dec): ^{1}H NMR (DMSO-d_6) δ 9.15 (s, 1H), 9.13 (s, 1H), 7.90 (m, 2H), 7.47 (m, 2H), 6.99 (m, 1H), 6.64 (s, 1H), 6.62 (s, 1H), 6.60 (m, 2H), 3.81 (s, 2H), 3.24 (s, 3H); LRMS (APIMS) *m/z* 408 $(M + NH_4)^+$.

1-(7-((3,5-Difluorophenyl)methyl)(2*H*,3*H*-benzo[3,4-e]1,4-dioxin-6-yl))-4-(methylsulfonyl)benzene (74). To a stirred mixture of **73** (0.400 g, 1.02 mmol) and 1,2-dibromoethane (0.21 g, 0.140 mL, 1.13 mmol) in dry acetone (50 mL) was added powdered potassium carbonate (2.96 mmol, 0.409 g). The mixture was heated at reflux for 4 h, then additional 1,2-dibromoethane (0.105 g, 0.070 mL) and potassium carbonate (0.205 g) were added, and the mixture refluxed overnight. The reaction mixture was cooled, filtered through Celite, and washed with acetone. The filtrate was evaporated under reduced pressure, and the resulting residue was partitioned between ethyl acetate and water. The organic layer was separated, washed with brine, dried over magnesium sulfate, and filtered, and the filtrate was evaporated to near dryness. Addition of ether resulted in the formation of off-white crystals of the title compound **74** (0.308 g, 73% yield): mp 160−162 °C; ^{1}H NMR ($CDCl_3$) δ 7.93 (td, J = 1.9, 8.4 Hz, 2H), 7.39 (td, J = 1.9, 8.4 Hz, 2H), 6.80 (s, 1H), 6.78 (s, 1H), 6.61 (tt, J = 2.3, 9.0 Hz, 1H), 6.45 (m, 2H), 4.34 (s, 4H), 3.82 (s, 2H), 3.12 (s, 3H); MS (APIMS) *m/e* 434 $(M + NH_4)^+$. Anal. ($C_{22}H_{18}SF_2O_4$) C, H.

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